

# DIABETES MANAGEMENT™

*The Complete Diabetes Disease State Management Resource*

## INSIDE

- **Waiting in the wings:**  
ACTOS, a new TZD-Class drug . . . . . 39
- **Calcium channel blockers:** Finnish researchers optimistic, despite U.S. criticism . . . 39
- **Y2K and insulin:** Will diabetics find a steady supply in 2000? . . . . . 40
- **Patient psychology:** Looking out for 'diabetes overwhelms' . . . . . 42
- **Foot care:** Research, advice, and a checklist to help you keep your patients' feet healthy . . . . . 45
- **News Briefs.** . . . . 46-48
  - Glucose monitor a step toward a synthetic pancreas
  - Two new Lilly products
  - Nephropathy and stroke risk
- **Inserts:**
  - Patient art
  - Foot screening form

**APRIL  
1999**

**VOL. 2, NO. 4  
(pages 37-48)**

American Health Consultants® is  
A Medical Economics Company

## FDA panel says Rezulin should not be used as monotherapy

*Experts say benefits to patients outweigh risks*

**R**ezulin remains on the market, but with some new restrictions and many caveats — after a Food and Drug Administration (FDA) advisory panel decided March 26 the benefits of the controversial insulin-sensitizing drug outweigh the risks of liver failure.

The recommendations of the Endocrinologic and Metabolic Drugs Advisory Committee, expected to be taken up by the full FDA in April, warn against the use of Rezulin as a monotherapy, but acknowledge its effectiveness when used for patients with particularly stubborn insulin resistance.

“This is not to be used ever as a first-line drug for diabetes,” says panel member **Jules Hirsch**, MD, senior physician at the Laboratory for Human Behavior and Metabolism at The Rockefeller University in New York City.

Rezulin, marketed by Warner-Lambert, has been linked to at least 28 deaths from acute liver failure.

The panel’s recommendation was greeted as a “good decision” by **Richard Kahn**, PhD, chief scientific and medical officer of the American Diabetic Association (ADA) in Alexandria, VA. “Monotherapy and the risk of adverse events are a concern. The use of monotherapy suggests that other therapies haven’t been tried,” he says.

In conjunction with either insulin, metformins, or sulfonylureas, Kahn says he believes the benefits to hundreds of thousands of patients who are particularly insulin-resistant outweigh the risks of liver damage.

Testimony from FDA epidemiologist **David Graham**, PhD, showed that at least 28 people have died from liver failure connected with the use of Rezulin since the drug was approved in January 1997. Seven others survived only with liver transplants, and five recovered without a transplant. However, Graham told the

### This month in *DM*

*D*iabetes Management keeps its readers at the cutting edge of the troglitazone controversy and the emergence of newer generations of the thiazolidinedione drug class. Reader opinion on this issue is welcomed. (See contact information, p. 47.) ■

## KEY POINTS

- FDA advisory panel says Rezulin (troglitazone) should not be used as a monotherapy.
- Panel rules benefits of Rezulin outweigh the risks of liver failure that caused at least 28 deaths.
- Patient education will be expanded to include warnings that those experiencing vomiting or nausea should contact their physicians immediately.

panel he believes the incidence of adverse liver reactions due to the use of Rezulin has been underreported. He conservatively estimates that only about 10% of the liver side effects have been reported, suggesting the incidence of acute liver failure is as high as one in 1,800 patients using the drug. Reports in the *Los Angeles Times* alleged 155 deaths might be tied to Rezulin. Approximately 750,000 patients have used it.

Last July, Warner Lambert inserted package liners alerting physicians to perform liver function tests at the beginning of Rezulin therapy and repeat them monthly for the first eight months of using the drug. With the start of month nine, liver tests should be done every two months for the remainder of the first year of Rezulin therapy, then performed periodically thereafter.

### ***Rapid failures can't be detected early***

However, Graham told the panel it took less than a month for patients to experience the most dramatic reactions to Rezulin, and as many as 75% of liver failures would be missed by monthly monitoring because of extremely rapid deterioration. He called these patients "rapid risers," who went into sudden acute liver failure in as little as four days after beginning Rezulin therapy.

"For most of these patients, jaundice was the first sign of trouble, and by then, the horse is out of the barn," he said, adding that encephalopathy

rapidly follows jaundice.

Some panel members suggested that patients need additional education when they begin taking Rezulin, and they should be advised to contact their physicians immediately if they experience nausea, vomiting, or jaundice.

Graham said the risk of complications increases the longer patients stay on troglitazone, and patients taking the drug have a risk of acute liver failure that is 50 times greater than that of the general population.

However, Warner Lambert argued that the risk seemed to diminish as patients take Rezulin for longer periods of time. The company said no cases of acute liver failure have appeared beyond 11 months of using the drug.

**Stephen Clement, MD**, an endocrinologist at the Georgetown University Medical Center in Washington, DC, argued on behalf of the ADA that "the benefits of Rezulin may outweigh its risks.

"Rezulin is a drug whose mechanism of action is not shared by any other approved glucose-lowering agent, and because of that fact, it has offered health care professionals an important advance in pharmacotherapy," Clement told the panel.

He said Rezulin has been "invaluable for countless individuals who, for many reasons, cannot achieve good glycemic control with the other drugs available."

Clement said the ADA trusts the FDA's expertise, not only in the matter of Rezulin, but in approving and reviewing new drugs, weighing benefits and risks in diabetes treatment.

March 23, the British equivalent of the FDA, the UK Medicines Control Agency, rejected an application by Glaxo Wellcome to reintroduce troglitazone to the British market. Glaxo voluntarily withdrew the drug from that market in December 1997 after reports of liver toxicity emerged in the United States and Japan. Glaxo applied for the reintroduction with recommendations of increased liver monitoring.

## COMING IN FUTURE MONTHS

■ Hypertension education: A neglected part of diabetes management

■ Management strategies for primary care physicians

■ Helping kids cope with dietary requirements

■ Prioritizing and managing comorbidities and complications

■ Age and diabetes: Pediatric, teen, adult, and geriatric issues

[For more information, contact the American Diabetes Association at (703) 549-1500. Contact the FDA's Center for Drug Evaluation and Research Endocrinologic and Metabolic Drugs Advisory Committee at (301) 827-7001.] ■

## Calcium channel blocker study fails to sway critics

*Older diabetics may benefit, but caution urged*

Critics are pouring cold water on a recent Finnish study that says the use of calcium channel blockers in older diabetic patients produces dramatic reductions in myocardial infarction and stroke.

The study, published in the March 4 issue of the *New England Journal of Medicine*, concludes that nitrendipine-based antihypertensive therapy produced markedly improved results for diabetic patients with hypertension.

The study conducted by Finnish researchers as part of the Systolic Hypertension in Europe (Syst-Eur) trial found that over two years, the use of calcium channel blockers by 492 diabetic patients produced these results:

- reduced systolic and diastolic pressure in diabetic patients by 10.3 and 4.5 mm Hg respectively;
- reduced overall mortality by 55%;
- reduced mortality from cardiovascular disease by 76%;
- reduced nonfatal stroke by 73%;
- reduced all cardiac events by 83%.

Among non-diabetic patients, the study showed respective reductions of 26% and 38% for all cardiovascular events and all strokes.

### KEY POINTS

- Finnish study shows benefits of calcium channel blockers in preventing stroke and myocardial infarction in elderly diabetic patients.
- Critics say trial was not definitive and repeat warnings that long-term calcium channel blocker therapy can worsen congestive heart failure and increase mortality for diabetic hypertensive patients.

## FDA gives Pioglitazone priority review status

While the Food and Drug Administration (FDA) is considering serious side effects of troglitazone, it has given priority review status to pioglitazone, another drug in the same class, thiazolidinediones (TZDs), which work by reducing insulin resistance and taking the stress off the pancreas.

Pioglitazone, developed by Takeda America Research and Development Center of Princeton, NJ, will be marketed in the United States by Eli Lilly and Co., under the brand name ACTOS.

Pioglitazone has been studied in human trials in the United States involving 2,500 subjects to date.

"Clinical studies indicate that ACTOS improves glycemic control in terms of fasting blood glucose and hemoglobin A1c," says **Roberta L. Schneider**, MD, Takeda's vice president for drug development and lead clinical researcher in the Princeton headquarters.

Schneider says ACTOS attacks insulin resistance, which "offers a more logical approach to treatment than many other therapies."

In January, the FDA granted priority review to rosiglitazone, another drug in the TZD class being developed by SmithKline Beecham under the brand name Avandia.

[Eli Lilly and Co. can be reached at (317) 277-1172. Contact Roberta Schneider at (202) 261-2873.] ■

A 1995 meta-analysis published in the journal *Circulation* showed that short-acting dihydropyridine calcium channel blockers seemed to provoke myocardial infarction (MI), as well as other data published in the intervening four years.

One of the authors of that original study was **Bruce Psaty**, PhD, MD, an internist and professor of medicine at the University of Washington in Seattle. Psaty is highly critical of the Finnish study's methodology and the quality of the medical care available to the study's subjects in Eastern Europe.

About half the patients in the Syst-Eur study were from Eastern Europe, which typically has "a lower quality of medical care," he says. "The CHF and stroke statistics in the study are typical of medical care in the U.S. in the 1960s. It looks like there were fewer events and higher numbers of fatalities, which suggests to me that either the investigators are missing mild events or the medical care system is missing them."

He points out that the Finnish study is “The one and only positive trial that has looked at calcium channel blockers.”

He and a group of fellow researchers have written a letter to the *New England Journal of Medicine* disputing the findings.

Some of the issues Psaty pointed out were:

□ Trials are compared though placebo patients were not similar.

□ The analysis was done through a posthoc subgroup analysis, rather than through a planned study, which “makes it difficult to know what it means.”

□ The study was conducted on a drug that is not available in the United States (nitrendipine, a dihydropyridine calcium channel blocker).

### **Researchers say study is supported**

The Finnish researchers, led by Jaakko Tuomilehto, MD, at the National Public Health Institute in Helsinki, Finland, argued their findings are supported by the 1991 Systolic Hypertension in the Elderly Program (SHEP), although the prevention of cardiovascular events and stroke was somewhat lower.

Other studies, such as the Appropriate Blood Pressure Control in Diabetes Trial (ABCD) showed higher incidence of MI among the nisoldipine group, but because patients received many different drugs at the same time, it is difficult to determine what accounted for the different risk.

The Finnish study underscores the importance of treating hypertension in diabetics, says **Sidney Smith**, MD, professor and chief of cardiology at the University of North Carolina Medical School in Chapel Hill and a past president of the American Heart Association.

“The article suggests that long-term calcium antagonists can be used among patients where other forms of antihypertensive therapy are not working,” he says. Smith notes that diuretics and ACE inhibitors were also being used by some patients, indicating that combination therapy may have had some bearing on the Finnish results.

He says the burgeoning incidence of hypertension may warrant the use of aggressive therapies such as calcium channel blockers, particularly among diabetics who are so susceptible to vascular disease.

[Bruce Psaty can be reached at (206) 731-5865. Contact Sidney Smith at (919) 966-0732.] ■

## **Does the Y2K bug threaten the insulin supply?**

*Producers are confident, pharmacists concerned*

**T**he Y2K computer glitch could quickly create life-threatening problems if it impedes the flow of insulin from manufacturers to patients who need it on a daily basis.

The two insulin manufacturers in the United States say not to worry. Meanwhile, the American Pharmaceutical Association Foundation and industrial consultants warn a bit of concern is appropriate, advising diabetics to begin slowly to accumulate an extra 30-day supply of essential prescriptions, just to be safe.

They all agree on one thing: If health care providers, pharmacies, and patients worry too much and begin to accumulate larger stockpiles than 30 days, they could create a “self-fulfilling prophecy,” resulting in a shortage of insulin.

The bottom line is that the Food and Drug Administration (FDA) is calling on pharmaceutical manufacturers to determine the vulnerability of the supply of prescription drugs in the face of the challenges presented — if computer programs won’t recognize the rollover to the year 2000.

Known by the shorthand Y2K, the problem arises from older computer systems programmed to recognize the year by two digits, as in “99” for 1999, which will refuse to function in 2000 because it will be unable to distinguish it from 1900. Business and industry are urgently implementing remedies for the problem, but some won’t finish before 2000, and others are dependent on vendors and those who could fail to be compliant in time.

Eli Lilly and Co. in Indianapolis, the country’s largest insulin producer, expects to be fully

### **KEY POINTS**

- Insulin producers take steps to ensure insulin stream will be uninterrupted after 1999.
- Pharmacists and others express concern and recommend patients keep an extra 30 days of medication on hand.
- Producers and pharmacists fear stockpiling will make insulin shortage a “self-fulfilling prophecy.”

Y2K-compliant by mid-1999 and Novo Nordisk Pharmaceuticals in New York City says its compliance will be complete by the third quarter of this year.

But spokeswomen for both companies caution their ability to produce insulin will be based on the assumption that computer-dependent municipal electric and water supplies remain uninterrupted.

"It's obviously a complicated issue," says **Susan Jackson**, spokeswoman for Novo Nordisk. "Our manufacturing process is very dependent on the delivery of electricity and water. If there was an interruption, all our manufacturing processes would stop and fermentation tanks would have to be emptied."

Novo's plant in Clayton, NC, will continue its ordinary insulin production, which keeps ahead by three to six months, not including "any stores already sold but not in patients' hands yet," Jackson says.

Lilly's spokeswoman, **Doyia Chadwick**, says at the beginning of the fourth quarter (Oct. 1), her company will have a 40- to 80-day supply of insulin based on normal buying patterns. She says Lilly always has a minimum of 45 days' supply of insulin on hand. She confirms that Lilly's Indianapolis manufacturing facility could be vulnerable to any power or water system failures from its surrounding community. "We're doing everything in our means to be ready."

### ***Stockpiling could create shortages***

Both firms say they are concerned that fearful suppliers and patients may create shortages by stockpiling supplies of insulin. "We're not recommending stockpiling in any way," Jackson says. "We believe patients will have the product they need."

Chadwick adds, "If everybody walks the walk, there will be no problem." But there are some who would rather be safe than sorry.

In a story published in the *Washington Post* on March 22, the American Red Cross recommended patients have several days to a week's supply of prescription medications on hand before the end of 1999.

**Ben Bluml**, RPh, the American Pharmaceutical Association Foundation's senior director for research in Washington, DC, takes a more cautious stance by recommending that consumers get a month ahead on their medications. "People should start stocking up in late summer or early fall," he says. "If people all start to get prepared

ahead of time, we'll all start to feel comfortable without creating an excessive burden on the supply chain."

Bluml says health care professionals should be sure the message is delivered in a way that "ensures responsible behavior." He called on pharmaceutical manufacturers to help instill "confidence in our system, but with technology the way it is, the supply chains are not that deep."

Bluml says health care providers recommending their patients get an extra month's supply of insulin should be aware that health plans often restrict prescription refills to one every 30 days, so patients may have to fight for reimbursement or finance the extra medications themselves.

The ECRI (Emergency Care Research Institute), a nonprofit global think tank in Plymouth Meeting, PA, is conducting its own research on Y2K issues, largely those involving the functioning of biomedical devices, and is offering telephone seminars on preparedness for health care professionals.

During a recent seminar, an informal poll showed that nearly half of the 179 participants (all health care professionals) intended to stockpile some medications in anticipation of some breaks in the supply line. Three out of four said they would save a week's supply or more, says **Tom Skorup**, associate director of the health support group at ECRI. Skorup says he is concerned about the manufacturers' ability to meet what appears to be a trend for at least moderate stockpiling.

"We can't foresee any real problems, but there's no way to be 100% sure," says **Tony Montagnolo**, ECRI's vice president for technological planning. "On the fringes, there are people who believe this is a giant hoax and others believe it may be the end of the world. We don't believe it's either." Yet, he adds, "There will definitely be problems. How serious they are depends on how well-prepared we are."

"If everybody behaves responsibly, we have no reason to believe Jan. 1, 2000, will be any different from Dec. 31, 1999," Bluml concludes.

At least one major mail order source of prescription drugs already has plans to stock up on insulin.

"We're just being prudent," says **Rick Lynch**, president of 50-50 Pharmacy in Carrollton, TX. "It doesn't hurt to have too much, but it will hurt if you have too little."

Lynch says he feels statements from Lilly and Nova are "ambiguous," and he needs to protect his patients, who buy 10,000 bottles of insulin a

month from 50-50. Of those, 95% of them are children. He's ordering extra stocks and bringing in extra refrigeration units.

[Contact Susan Jackson at (212) 867-0123, Doyia Chadwick at (317) 277-6990, Ben Bluml at (800) 237-2742, and Tom Skorup and Tony Montagnolo at (610) 825-6000.] ■

## Helping patients cope with impact of diabetes

*Look for signs of depression regularly*

The technical name might be diabetes mellitus, but one clinician has dubbed it "diabetes overwhelmingus."

"A diagnosis of diabetes requires a patient to make hundreds of decisions a day related to the disease. It can all be overwhelming," says **Richard Rubin**, PhD, assistant professor of medicine and pediatrics at Johns Hopkins School of Medicine in Baltimore.

Rubin tells the story of his son, diagnosed with Type 1 diabetes 20 years ago at the age of 7. "He told me recently that he hasn't gone 15 minutes without thinking of his diabetes since then," Rubin says. "That's a heavy burden for anyone."

Diabetes is an unusual disease because it requires patients to manage their own disease 99% of the time, he adds.

The disease requires total lifestyle change, regardless of the age of the patient. An adult diagnosed with Type 2 diabetes has to change diet, exercise, and general health habits. Children diagnosed with Type 1 can involve the whole family in their care, considering how important it

### KEY POINTS

- Diabetes can be a psychologically overwhelming disease for the patient and his or her family.
- Patients and family members, where appropriate, should be screened regularly for depression.
- Experts say empowering patients and family members to manage their disease helps alleviate depression, anger, guilt, and denial.

is to eat the proper diet and take medications properly.

It's not surprising that many diabetics and their families begin to suffer psychological setbacks, sometimes even serious psychological disorders that become comorbidities of their disease.

Among the most common psychological effects of diabetes are:

- ✓ clinical depression, especially among Type 2 diabetics and older children with Type 1;
- ✓ anger at being saddled with a disease that changes lives forever;
- ✓ family dysfunction triggered by the lifestyle changes required by the disease;
- ✓ denial often manifested by statements such as "I had a touch of sugar once, but now I'm OK."

In the following articles (**below and p. 44**), *Diabetes Management* examines the unique psychological conditions often associated with Type 1 and Type 2 diabetes and some ways to treat them. ■

## Family affair: Managing a child with Type 1 diabetes

*Coping tools can have profound impact*

A diagnosis of diabetes in a child changes that family forever. "There's no vacation, no respite. Nobody else can do it for you. You always have to pay attention to the clock," says **Sandy Puczynski**, PhD, director of research and evaluation for the Medical College of Ohio in Toledo and chairwoman for research of the Juvenile Diabetes Foundation.

"When a child gets diabetes, it's much as though the whole family gets the disease because everyone has to deal with it," says **Christine Ternand**, MD, a pediatric endocrinologist at the University of Minnesota Hospital System in Minneapolis.

Both Ternand and Puczynski advocate individual contact with patients and their families as well as group therapy. Referral to a behavioral therapist is recommended if the situation is serious enough to warrant it.

Ternand teaches coping skills to the entire family that focus on a model of grieving for the child that will never exist again through the classic

stages of death and dying. “Some feel they have fallen into a black hole, a place of not feeling and denial,” she says. “Another stage is guilt for having developed the disease, another is fear of the condition worsening, and finally, there is acceptance,” she explains.

### ***The need to grieve***

The grieving for the life a child might have lived without diabetes is profound “because there are losses at the ages of 6, 12, 16, as there are things the child can’t do because of diabetes,” Ternand says.

She remembers a woman in her 40s who came to her office one afternoon in support of a friend whose young daughter had recently been diagnosed with diabetes.

“When I told them we needed to say goodbye to the child who doesn’t need shots, she began to sob,” Ternand says. “She cried for 40 minutes, grieving her own ‘self’ as a child diagnosed with diabetes more than 30 years before and never having had the opportunity to grieve.”

Unresolved grief may look very much like depression, she adds. “People become afraid to feel their sadness, anger, and fear. They can’t move on through the cycle until they do.”

At the acceptance stage, she says, people begin to look at “what’s the plus?”

“I truly believe that everything has a blessing,” Ternand says. “So I help them see that the family is pulling together. Maybe the whole family is eating healthier, that the child is becoming more responsible, that a child met her best friend at diabetes camp. I recently had a boy who discovered he was eligible for a scholarship because he is diabetic.”

“Some people don’t want to talk to me after I introduce this idea, but I have planted the seed, even if it takes 10 or 15 years to sprout,” she says.

Puczynski adds that diabetic children often grow up to be extraordinary adults because they mature at an early age.

Ternand works with an art therapist to help patients and their families express their feelings “at an awesome level.” She recalls a little girl who drew a picture of herself and a friend walking down the street with a fence between them. “That fence was diabetes,” Ternand says. **(See samples of patient art, inserted in this issue.)**

Diabetics and their families frequently express rage at the unfairness of the disease, Ternand says, recalling a diabetes camp counselor who was “the

sweetest girl you’d ever want to meet and she drew an ax murderer chopping up diabetes.”

She stresses the importance of being aware of the impact of diabetes on siblings. She remembers a child who drew the entire family in red except one child who was blue and crying huge tears. “That was the sibling who felt she had been excluded from something important.” The father of one young patient drew an atom bomb when asked to portray the impact of diabetes on his life, she says. “Diabetes is a challenge for the entire family, and we need to treat it as such.”

Both Puczynski and Ternand say diabetes can cause an already dysfunctional family to fall apart, in which case the burden of managing the disease will fall upon the shoulders of one parent — most often the mother.

Parents of diabetic children face multiple challenges. Puczynski says it’s difficult for a parent of an infant or toddler who must cause the child pain through repeated finger sticks and injections the child does not understand. “Even when parents know it’s for the child’s good, it is hard to hurt a child,” she says.

It’s also hard to see a child lose his freedom, to lose his spontaneity, and as the teen-age years arrive, to address compliance issues in children who resent being different, who don’t want to take injections when they are with their friends, she says. Yet, she adds, teen-agers don’t want to embarrass themselves by having a hypoglycemic incident in public.

### ***When to let go***

Ternand and Puczynski agree one of the greatest challenges for health care professionals dealing with young diabetics is to help parents know when it is time to allow the child to take more responsibility for the disease and when to assert more control. They also agree the best approach to caring for any child with diabetes is to take an attitude of support, not one of criticism.

It’s very dangerous to threaten a child with dire warnings about the consequences of failing to maintain strict control, Puczynski warns. And when the going gets rough, Ternand recommends referral.

“Children with diabetes should be seeing people who deal with children with diabetes,” Ternand concludes.

*[Sandy Puczynski can be reached at (419) 383-5507. Contact Christine Ternand at (651) 641-3165.] ■*

# Depression undertreated in adult diabetics

## *Empowering patient improves compliance*

**R**ichard Rubin, PhD, says nearly half of his diabetic patients plunge into clinical depression. “Depression is a severely underdiagnosed and undertreated problem for people with diabetes,” explains the assistant professor of medicine and pediatrics at Johns Hopkins School of Medicine in Baltimore. “It’s uniquely devastating because it can lead them into a downward physical spiral.”

He says depressed patients with diabetes are more likely to have complications probably because they don’t care for themselves or their disease as well as they should. “Some of them say, ‘To hell with it all,’” Rubin says, remembering a patient in a group therapy session who told him that those with the “hell with it” attitude often wind up in a living hell.

Depression tends to increase with the seriousness of the disease and as complications set in, says **Beth Venditti**, PhD, licensed psychologist, coordinator of lifestyle resources in the Diabetes Prevention Program at the University of Pittsburgh.

“I see people with borderline diabetes, at the earliest stages, so I don’t see as much depression,” Venditti says. “That in itself is another strong argument for prevention of diabetes.”

She points out, “A diabetic person isn’t going to automatically be in the mental health system, so it’s important for endocrinologists, clinicians, and diabetes educators to become very familiar with the criteria for depression so they can treat it or make the appropriate referrals.” (See box for list of questions to ask your patient, at right.)

## *Treat depression as a separate disease*

Depression should not be treated casually, Rubin adds, and it must be treated as a disease separate from diabetes. Treating diabetes, even with good control, doesn’t necessarily answer the problem of depression, which may require therapy or medication.

Health care professionals who treat diabetic patients should screen them for depression at every visit. “We need to recognize when somebody is depressed and treat them with appropriate medications, counseling, and cognitive

behavioral therapy,” he says. Among diabetics, Rubin adds, “Depression is common, severe, debilitating, and treatable.”

Other emotions are significant as well. “People tell me they are angry they have to deal with this disease,” Venditti says. Anger, like depression, lessens the likelihood of patient compliance.

Denial gets in the patient’s way as much as anger or depression and may be triggered by a lack of education among those who have been told they have “a touch of sugar” and think they have “recovered” from diabetes.

Add that to the guilt many patients feel for not sticking with their diets or exercise plans, and compliance suffers even more, she says. It’s tough to urge patients who feel that way to make the lifestyle changes necessary to manage their diabetes without triggering the syndromes of guilt, anger, denial, or even depression.

## *Reaching out*

Rubin’s answer is to reach out to struggling patients by asking, “What’s the hardest thing for you right now?”

He follows that with, “What have you done to change?”

The final question, which Rubin says requires a very specific answer is, “What do you want to change?”

For example, he recalls a patient who told him he was a “grazer” and spent several hours an

## Screening for Depression

**E**xperts recommend asking diabetic patients the following questions:

1. Are you feeling sad or hopeless?
2. Are you more tearful than usual?
3. Are you sleeping more than you once did?
4. Has your appetite or weight changed since you were diagnosed?
5. Have you lost interest in things that once interested you?
6. Has your level of enjoyment and pleasure declined?
7. Do you feel guilty or bad about yourself?
8. Are you having troubles or concerns?
9. Do you have any thoughts about hurting or killing yourself?

Source: Richard Rubin, PhD, Johns Hopkins School of Medicine, Baltimore.

evening eating a little bit of one thing, then a little bit of another thing. “The key was for me to help him see he had the solution to the problem,” Rubin says. “I asked him about the times he didn’t graze and how he felt.”

“Inevitably when you ask a patient about the times he was in compliance, he will say something positive,” he says. The way to increase the amount of compliance is to be “facilitative rather than directive,” says Rubin, who is author of several books, including *Practical Psychology for Diabetes Clinicians*.

Empowering patients to manage their disease lies at the heart of managing the psychological effects of diabetes, he says. “Engage their expertise. They are experts in their own lives. That’s fundamental. The job is not to manage diabetes, but to help [patients] manage their diabetes. That’s what helps keep them from getting overwhelmed,” he says.

[Richard Rubin can be reached at (410) 243-6565 and Beth Venditti at (412) 383-2478.] ■

## Diabetic feet require regular care, attention

*New treatments may help prevent amputations*

Vigilance has long been the watchword in treating the feet of diabetic patients. Even so, up to 15% of all people with diabetes suffer a lower extremity amputation sometime in their lifetimes.

And as the incidence of diabetes increases and the diabetic population ages, the rate of foot ulcers is increasing at an even faster pace with the number of amputation increasing 29% in the 1980s.

Yet, the American Diabetes Association (ADA) says simple and inexpensive interventions can decrease the amputation rate by 85%. There are also some interesting new treatments already in use that can provide relief in extreme cases just short of amputation.

“The key is prevention. If we can identify those at high risk and target service to them, we’ll improve outcomes and prevent amputations,” says **Lee Sanders**, DPM, the ADA’s vice-president for health care and education who practices at the VA Medical Center in Lebanon, PA. (See **patient foot care checklist, inserted in this issue.**)

The ADA recommends an annual foot exam

for all patients with diabetes and more often for those at high risk.

The following are risks to foot health:

- Compared to the general diabetic population, those over 65 who have had the disease for more than 10 years face twice the risk of needing an amputation.

- Males have a 1.6-fold increased risk of ulcers and as much as 6.5-fold risk of amputation compared to females.

- African-Americans and Hispanics have about twice the risk of amputation, and some Native American tribes have a four-fold higher rate than whites with diabetes.

- Living alone presents up to 3.8-fold increase risk of amputation.

- Comorbid conditions, including diabetic retinopathy, renal disease, and macrovascular disease such as coronary artery disease are major risk factors.

- Lack of patient education on foot-care methods more than triples the risk of amputation.

### Simple screenings

Sanders says a clinician should check patients’ feet at every checkup, examining the skin for breaks, color changes, and overall integrity and texture. The clinician should also look out for any deformities to the feet and take pedal pulses.

He says the simplest screening technique is the use of a Semmes-Weinstein 5.07 monofilament used to test sensation in the foot, which is available at most medical supply centers. “Every physician who is seeing diabetic patients should have one of these in his pocket,” says Sanders.

“If they can’t feel that monofilament, then they’ve lost their protective sensation and they are at high risk for foot ulcers and possible eventual

### KEY POINTS

- Risk of foot ulcers increases in:
  - people who have had diabetes more than 10 years;
  - males;
  - patients who have poor glucose control;
  - those who have cardiovascular, retinal, or renal complications.
- Several new treatments for foot ulcers are available, including a new surgical technique, a healing gel, and an extreme form of debridement with the help of maggots.

amputation,” says **Vincent Giacalone**, DPM, a podiatrist at the Hackensack University Medical Center and the Pascack Valley Hospital in Westwood, NJ. He also is a member of the diabetes advisory committee of the American Podiatric Medical Association.

Giacalone explains the importance of performing such tests because patients might not notice the gradual and painless loss of sensation on their own.

Beyond the simple screening devices that virtually any clinician can perform, signs of abnormality should be a signal for referral to a podiatrist or an orthopedist for further investigation.

Many specialists have pressure plate sensors in their offices, which can help determine weight distribution and detect pressure points that could cause an ulcer. “The patient walks across a gait platform that picks up pressure on the ball of the foot. When they place a lot more pressure on the ball of the foot, they are vulnerable to ulcers,” Giacalone says. The key, he says, is to get the pressure off, whether through inserts or special shoes. Once an ulcer develops, the treatment is far more difficult, he says, and signals the time when a primary care physician should consider a referral if one has not already been made.

“Most often, we see patients with ulcers that are not responding to care by primary care physicians because they are not getting the pressure off. Getting the pressure off is the key to healing those ulcers,” he adds.

Treatment involves weekly debridement, healing sandals, and sometimes, total contact casts replaced weekly for several weeks.

### ***Looking at the unconventional***

In cases of stubborn ulcers that do not respond to conventional treatment, two new treatments have gained considerable attention.

The first is Regranex, a unique bioengineered gel that speeds healing. “It works very well; I like it,” says Giacalone.

Sanders says Regranex can play a “useful role,” but its high cost precludes it from being a treatment of first choice. “It should be for those who haven’t done well with the simpler approaches,” he says. (The medicine costs \$350 to \$400 per tube; patients usually need two tubes to treat their feet over a two-month period.)

Giacalone says in a year or so he expects bioengineered skin cultured from the foreskins of circumcised infants to become available.

Research is showing maggot therapy may become useful as well. But even though the creatures are cultured under sterile conditions, patients can be squeamish about inserting live maggots into their open ulcers. An Israeli study showed maggots applied from two to five times a week for 24 to 72 hours completely debrided 67% of foot ulcers within six weeks of use. Healthy new tissue had grown over the wound.

Giacalone says the treatment works because “maggots will only eat dead tissue,” but adds, “Generally, we like to use a scalpel.”

Other treatments require more tools than a scalpel. Perhaps most unconventional of the new treatments is a dramatic surgery called diabetic foot salvage and used for Charcot’s foot (a condition where bones in the foot collapse).

**R.J. Sullivan**, MD, an orthopedic surgeon at the University of Connecticut Health Center in Farmington, has had “good success” with the complex procedure that involves screws and wires in the bones and finally a plantar plate. He says he’s had a 75% to 80% success rate with the procedure, but cautions, “It’s a last attempt to salvage the foot before amputation.”

Prevention is still the best way to tackle these problems, says Sanders, who says many of the serious diabetic foot problems can be stopped before they start with a simple foot exam every time a patient visits the primary care provider.

*[Lee Sanders can be reached at (717) 228-5952. Contact Vincent Giacalone at (201) 445-2000 and R.J. Sullivan at (860) 679-6600.] ■*

## **NEWS BRIEFS**

### **Developing an artificial organ — getting closer**

**R**esearchers trying to develop a synthetic pancreas may be one step closer to success, now that a continuous glucose monitoring system received conditional Food and Drug Administration (FDA) approval in March. One day, the technology may be used with an insulin pump, in

order to restore some of the functions a healthy organ would do on its own.

The monitor, developed by MiniMed in Sylmar, CA, is composed of a sensor inserted subcutaneously to monitor glucose in interstitial fluids. A thin wire attaches it to a pager-sized glucose monitor. Its readings can then be downloaded into a computer.

The FDA approved use of the monitor under physician supervision, and it is intended to be worn for three days to provide a comprehensive record of glucose fluctuations, says **Bob Murtfeldt**, MBA, a chemical engineer and biochemist who is MiniMed's director of business development.

The monitor includes an event menu that can mark mealtimes, exercise periods, insulin injections, and other data important to the management of the disease.

"Endocrinologists tell us there isn't anybody they wouldn't want a three-day report on, as opposed to three or four snapshots a day you get from a glucose monitor," Murtfeldt says.

MiniMed also manufactures insulin pumps. he says, "An artificial pancreas is our long-term goal, to combine the pump and the sensor to insulin can be delivered on demand. This is a step in that direction."

MiniMed is working on the first-generation combined pump and monitor, and the project is about three years away from human trials, Murtfeldt says. The company hopes to receive approval for consumer purchase and use of the Continuous Glucose Monitoring System soon.

"It will save a lot of finger sticks with just a small needle-injected sensor," Murtfeldt says. ▼

## Lilly launches insulin pens and glucagon injectibles

**E**li Lilly and Co. of Indianapolis has launched two new products important to diabetes management.

Recombinant glucagon for use in severe hypoglycemic events has replaced the company's animal-source glucagon product and was expected to be available in pharmacies in March.

The Humulin 70/30 (70% human insulin isophane suspension, 30% human insulin), Humulin N, and Humalog injections are intended to simplify insulin delivery.

The pre-filled disposable pens hold 300 units of

insulin. No refrigeration is necessary after the first use. The pocket-sized pen has a magnified dosage window to dispense precise quantities of insulin. It's designed to improve glycemic control in patients with irregular schedules. ▼

## Study links nephropathy with familial risk of stroke

**A** Scottish study published in the March issue of *Diabetes Care* links a familial history of stroke and vascular disorders to diabetic nephropathy.

Parents of patients with diabetic nephropathy had a four-fold increase risk of stroke and a significantly shorter life span than parents of controls.

Researchers at the Royal Infirmary of Edinburgh NHS Trust said, "This supports the hypothesis that a common hereditary risk factor predisposes to both vascular death and diabetic renal disease."

*Diabetes Management*™ (ISSN# 1098-0032) is published monthly by American Health Consultants®, 3525 Piedmont Road, Building Six, Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Application to mail at periodical rates is pending at Atlanta, GA 30304. POSTMASTER: Send address changes to *Diabetes Management*™, P.O. Box 740059, Atlanta, GA 30374.

### Subscriber Information

Customer Service: (800) 688-2421 or fax (800) 284-3291, (customerservice@ahcpub.com). Hours of operation: 8:30-6:00 Monday-Thursday, 8:30-4:30 Friday, EST.

Subscription rates: U.S.A., one year (12 issues), \$259. Outside U.S., add \$30 per year, total prepaid in U.S. funds. One to nine additional copies, \$207 per year; 10 to 20 additional copies, \$155 per year. For more than 20 copies, contact customer service for special arrangements. Missing issues will be fulfilled by customer service free of charge when contacted within 1 month of the missing issue date. Back issues, when available, are \$43 each. (GST registration number R128870672.)

Photocopying: No part of this newsletter may be reproduced in any form or incorporated into any information retrieval system without the written permission of the copyright owner. For reprint permission, please contact Karen Wehwe at American Health Consultants®, Address: P.O. Box 740056, Atlanta, GA 30374. Telephone: (404) 262-5491. World Wide Web: <http://www.ahcpub.com>.

Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

Editor: **Kathleen Barnes**: (828) 883-5695, (wolfeagle@citcom.net).

Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@medec.com).

Executive Editor: **Park Morgan**, (404) 262-5460, (park.morgan@medec.com).

Managing Editor: **Valerie Loner**, (404) 262-5536, (valerie.loner@medec.com).

Associate Managing Editor: **David Flegel**, (404) 262-5537, (david.flegel@medec.com).

Production Editor: **Ann Duncan**.

Copyright © 1999 by American Health Consultants®.

*Diabetes Management*™ is a trademark of American Health Consultants®. The trademark *Diabetes Management*™ is used herein under license. All rights reserved.

### Editorial Questions

For questions or comments, call **David Flegel** at (404) 262-5537.

(See: *Lindsay et al. Diabetic nephropathy is associated with an increased familial risk of stroke. Diabetes Care 1999; 22:422-425.*) ▼

## Genetic link between diabetes and obesity

What if your patients could eat all they like and take a little pill to suppress genes that trigger insulin resistance and weight gain?

Sound like a dream?

That little pill may still be a decade or more away, but important new findings from the Merck-Frosst Center for Therapeutic Research in Pointe Claire-Dorval, Quebec have turned attention toward suppression of the gene protein tyrosine phosphatase-1B (PTP-1B) as the wave of the future of treatment of diabetes.

Lead researcher **Brian Kennedy**, PhD, a molecular biologist and senior research fellow at Merck-Frosst says the discovery “will open a whole new area of diabetes research. I have a pretty good feeling this may be the underlying cause of resistance in Type 2 diabetes.”

His excitement is mirrored on a slightly less enthusiastic level by **Harvey Ketzeff**, MD, chief of the division of Endocrinology at Long Island Jewish Medical Center in New Hyde Park, NY.

“This is further evidence that genetic influences are critical in the development of diabetes and obesity,” Ketzeff said. “There are many genes involved in insulin action, but understanding how this gene works will help us learn how to become sensitive to insulin.”

Kennedy’s research team was able to remove the PTP-1B gene by using altered stem cells in a tissue culture in mice. The altered mice and a control group were fed the same high-fat high-calorie diet.

“In the fed state, PTP-1B mice had a significant 13% reduction in blood glucose concentrations. . . . The PTP-1B mice had circulating insulin concentrations that were about half those of the control-fed animals.” Kennedy wrote in the study published in *Science* on March 5.

Kennedy said he was surprised to find the mice did not gain weight. “During the 10 weeks the mice were on this diet, male and female wild-type littermates rapidly gained weight, whereas PTP-1B mice were substantially protected from diet-induced weight gain.”

### EDITORIAL ADVISORY BOARD

**Consulting Editor:**  
**Ralph R. Hall, MD**  
Emeritus Professor of Medicine  
University of Missouri-Kansas  
City School of Medicine  
Kansas City, MO

**Nancy J.V. Bohannon, MD**  
Associate Clinical Professor  
Family and Community Medicine  
and Internal Medicine  
University of California  
San Francisco

**H. Peter Chase, MD**  
Director of the Clinical Division  
Professor of Pediatrics  
Barbara Davis Center  
for Childhood Diabetes  
University of Colorado  
Health Sciences Center  
Denver

**Raymond Hintz, MD**  
Division Chief and Professor  
Pediatrics and Endocrinology  
Stanford University  
School of Medicine  
Stanford, CA

**John C. McDonald, RN, MS, CPHQ**  
Vice President  
of Clinical Services  
Physicians Community Health, LLC  
Brentwood, TN

**Kathryn Mulcahy, RN, MSN, CDE**  
Director  
Fairfax Hospital  
INOVA Diabetes Center  
Fairfax, VA

**Barbara Schreiner, RN, MN, CDE**  
Associate Director  
Diabetes Care Center  
Texas Children’s Hospital  
Houston

**Charles A. Wells, PhD**  
Director  
Diabetes Complications  
Research Program  
NIDDK  
Bethesda, MD

“I wouldn’t be surprised if some people are genetically protected against diabetes and obesity,” Kennedy says. “This is the first time there has been such a link found and it’s a good target to develop drugs against.”

[Contact Brian Kennedy at (514) 695-8221.] ■

## CE objectives

After reading this month’s issue of *Diabetes Management*, CE participant should be able to:

- identify particular clinical, administrative, education or managerial issues related to the disease management of diabetes patients;
- describe how those issues affect diabetes patients, diabetes management programs, and diabetes costs;
- cite practical solutions to disease management problems associated with diabetes, based on overall expert guidelines from the National Institutes of Health, the American Diabetes Association, the American Association of Diabetes Educators, or other authorities, or based on independent recommendations from clinicians at individual institutions. ■