DIABETES CLOSE UP

Diabetes Close Up
August 2006, No. 60
AADE Preview: Updates and Analysis With Industry Leaders

T h e S h o r t e r V e r s i o n

From the Editor:

Summer is so the best, and DCU's favorite season, for a million reasons*! First, there is the fabulous triumvirate of conferences with the ADA/CWD/AADE meetings in June/July/August, closely followed by EASD in early September. Second, our team expands by a few people every summer as new associates (summer and permanent) jump right into research and writing.*[1] *Third, summer brings holidays, and rest, and perspective – my family has been thinking so much this summer about how lucky we are, and I hope you're in that position as well.*

So, as you might imagine, we're geared up for Los Angeles *– eight of us who work on Diabetes Close Up are headed down this week to take in the annual American Association of Diabetes Educators meeting. I have always loved this event. The first AADE meeting I attended was in the old days, when I had just started my Wall Street equity research work, and I had a position on a team analyzing medical technology stocks. In those days, the stocks included J&J, Abbott, BD, and Medtronic – Medtronic before the company had committed to diabetes and purchased MiniMed, Abbott before it had purchased TheraSense, J&J before it had purchased Animas – and in fact, this was before TheraSense, Animas, and Insulet had even been founded, or perhaps, just barely. So I remember seeking ways to attend this meeting. That year, it was in Minneapolis, and I was supposed to be working on a financial stent mode. After I requested permission to go to the meeting ("…*we could do a diabetes industry report*!") and was summarily rejected, I announced I would take a vacation day that Friday (that Thursday was still earnings season so no way could I get out of Dodge), and I flew up to take in the meeting. Even though paying for a last minute flight and for the entrance fee on a junior salary was difficult, I'll never forget how generous educators were with their time and energy, nor will I forget just how much I learned. Since then, in nearly a decade, I haven't missed a single AADE, for there is no better place to discuss what is* really *happening in patient care. Our schedule is on our website (www.closeconcerns.com), and our in-depth preview is inside. We'll have subscriber-only blogs all week, and we'll be on the hunt for news on new products in particular (incretins, inhaled insulin, continuous monitoring, etc).*

In honor of AADE this month, we had the opportunity to interview two remarkable educators *– Dr. Jane Kadohiro, former AADE president (who has had type 1 for over 50 years) and Geralyn Spollett, the ADA 2006 educator of the year. We thank them both, mightily.*

Summer reading issue/three private companies funded: *Inside, we have our largest-ever company update section – 26 companies! If that weren't enough, we also note there were announcements of three new companies funded in the last month alone – Biodel, Veralight, and Glumetrics. More on these inside…*

Speaking of reports, above – we've just published our Diabetes Round Up II, our 600-plus-page report synthesizing diabetes developments over the past 18 months! *Much has happened in this past year and a half. This volume, Diabetes Round Up II, is intended as a comprehensive guide to the exciting events of*

[1] If any of you know college students who might be drawn to work in diabetes and who would like a summer in San Francisco in 2007, please ask them to write me directly at summer@closeconcerns.com. We attract incredible students planning on careers in medicine – five of our former associates are now immersed in medical school, at Stanford, Emory, Columbia, Harvard, and UCSF.

2005 and 2006 – what they mean for patients, companies, payers, and investors. Inside the report:

- *In-depth reviews of 25 conferences, both large and under the radar screen (ADA, ADA Postgraduate Sessions, AADE, AACE, EASD, DTT, NAASO, the 1st Annual Amsterdam Diabetes Forum, the Canadian Diabetes Association; 1st International Conference on Pre-Diabetes and the Metabolic Syndrome; AIDPIT: Artificial Insulin Delivery Systems, Pancreas, and Islet Transplantation; ACE/AACE Consensus Conference on Inpatient Diabetes and Glycemic Control; and the Levine Symposium, among others)*
- *Detailed financial models for the $6 billion blood glucose monitoring and $1 billion insulin pump markets*
- *An-depth drug pipeline database of 40-plus companies developing 250 diabetes and obesity drugs*
- *Our selection of the top 50 diabetes-related articles in medical journals over the last year (JAMA, NEJM, Diabetes Care, The Diabetes Educator) and detailed reviews of each*
- *Our reports on the major analyst meetings over the last 18 months (AstraZeneca, Animas, BMS, Lilly, Medtronic, Merck, Roche, Pfizer, Sanofi, etc.)*
- *A detailed calendar of 30 important upcoming diabetes meetings in 2006 and 2007*
- *The best of DCU: our top five stories from DCU #1 - #55*
- *The Close Concerns High Five Awards: our own view of the top five diabetes products introduced over the last 18 months*

The report is $6,500, and there is a 10% discount (please use promotion code AADE when ordering online) for any orders received before AADE is over. For a detailed introduction to the report as well as ordering information, please see our home page at www.closeconcerns.com.

–Kelly L. Close

In this issue:

- **Novartis 2Q06: Galvus in the works …**
- **Northfield Laboratories: PolyHeme for islet transplants**

8. **Literature review column: Hyperglycemia management for type 2s – *page 27***
9. **dLife shows you must not miss – the upcoming three top episodes to look out for… – *page 29***
10. **Upcoming Conference Preview – *EASD and IDF – page 29***

<u>Quotable Quotes from August's DCU:</u>

From Dr. Jane Kadohiro, former AADE president

- "*[Diabetes is] becoming a household word. I know early on, I could not get the media to do anything with it because it was boring. There was nothing sexy about it. And now everywhere you turn, you're hearing about diabetes. I think in some ways the ability for companies to advertise their drugs and products – consumer advertising – has made a difference.*"
- "*The CEO of the insurance company or the health plan is there for today's bottom line. And if at the end of the year when they close their books, if their bottom line is not improving, they're not going to have a job come another year or two. So when they put resources into prevention, they are not going to get an immediate payoff. The payoff comes in three or four years. Some studies have actually shown you can start at least breaking even in two years with all of the preventive activities covered. But the CEO is worried about the bottom line this year."*

From Geralyn Spollett, 2006 ADA Educator of the Year

- "*We have difficulty taking the mask off diabetes… We just don't want to face it. Even the ADA for years refused to use any kind of what they termed scare tactics to talk about diabetes because they felt that it was disabling to the population with the disease. And so we've spent a long time noodling and doodling around diabetes to make it more acceptable to the people that have it, which I think in turn has come back to slap us in the face when we talk about it as a serious disease.*"
- "*One of my patients that works very hard at his diabetes was working as an umpire for a little league game. And he was checking his blood sugar and eating and doing all the things that he normally does to keep his blood sugar where he wanted it during the game. And then on a very hot day, he passed out because his blood sugar went down into the 30s. It caused quite a stir. They had to get the ambulance; the kids got all worked up. And what he said to me was very profound. He said, 'You know, my victories are always private, and my defeats tend to be public.' And I have to tell you that there hasn't been a day that's gone by that I haven't thought of that and what that means.*

Dr. David Geldmacher (on glitazones for Alzheimer's)

- "*Based on the proposed mechanisms of action—and frankly, we don't know how the medicine is working and whether it's working by one or more than one mechanism—but based on the proposed mechanism of action, there are reasons to believe that the drug may have prophylactic effects, that is, either to delay the onset or reduce the risk for Alzheimer's disease."*

Blogwatch - See below for blogs since our last monthly newsletter. You can see any update online at http://www.closeconcerns.com/ as well as subscribe to the RSS blog feed.

- **August 3: Novo brings out big guns - suing Pfizer. Oh, and excellent revenue/earnings results...**
- **July 26: GSK on fire with Avandia**
- **July 26: Poll shows that more Americans find childhood obesity to be a major problem**
- **July 17: Medtronic receives approval for stand-alone sensor**
- **July 13: Avandamet as first line therapy...?**
- **July 6: Bayer buys Metrika**
- **July 5: JDRF Bay Area Research Meeting highlights new direction for organization**
- **June 26: Nastech and Amylin ~ early stage deal**
- **June 25: Metabolic Syndrome - It's not over yet!**
- **June 23: New York Times weighs in on new diabetes medicine ~ a billion isn't so hard to reach!**

T h e L o n g e r V e r s i o n

1. AADE preview and talks with leading CDEs Jane Kadohiro and Geralyn Spollett

As Speaker of the House, Newt Gingrich was one of the most divisive figures in recent political history, but he found common ground with the sprawling diabetes community. Learning about the disease after his mother-in-law's diagnosis, Gingrich spearheaded major funding for diabetes research and became a strong advocate for preventive care. Now, with Gingrich pondering a presidential run in 2008, he will be the keynote at the AADE in Los Angeles, which takes place August 9-12 at the Los Angeles Convention Center. Some say Gingrich is branching out to new constituents. We say he's returning to his base (kind of). Either way, his speech on Wednesday morning -- "Saving Lives & Saving Money: Transforming Health and Healthcare in the 21st Century" – is worth catching, no matter what you think of the guy in other respects (we'll leave it at that). To prepare for the entire meeting, we have pored over the schedule and have our top ideas for sessions for you to attend. The complete schedule can be found on our homepage for subscribers and at http://www.aadenet.org/ContinuingEducationCE/AnnualMeetings.shtml.

It will be hard to choose among the many exciting corporate symposia following Mr. Gingrich's talk. Amylin's symposium, entitled "Current and Future Perspectives on the Role of Hormonal Interplay in Glucose Homeostasis," will be presented by Stephen L. Aronoff, MD, Steven V. Edelman, MD, and Davida F. Kruger, MSN, APRN-BC, BC-ADM. Outstanding team and we personally wouldn't miss this one after what we've learned about Symlin and Leptin. Medtronic's symposium will focus on reshaping diabetes management through real-time continuous glucose monitoring, as presented by Francine R. Kaufman, MD, and Allison K. Wick, MSN, ARNP-BC, CDE – Dr. Kaufman ran some of these trials and will no doubt have great insights as always. The Novartis symposium will focus on the impact of incretin therapies in Type 2 diabetes and will be presented by Vivian Fonseca MD, Daniel Porte, Jr., MD, and Virginia Valentine, CNS, BC-ADM, CDE. This program will review incretin physiology and current clinical data on incretin-based therapies currently available and in development, a topic that continues to consume us. An interactive panel discussion promises to elucidate where incretins are likely to best fit in current treatment approaches. Eli Lilly is sponsoring a symposium on patient education and insulin therapy for improved glycemic control presented by Deborah Hinnen, MN, Karmeen Kulkarni, MS, RD, BC-ADM, CDE and Cameron C. Lindsey, PharmD, BC-ADM. Novo Nordisk's symposium, entitled "Why & How of Early Intervention with Insulin Analogs," will be presented by James R. Gavin III, MD, PhD, and Peragallo-Dittko, MA, RN, BC-ADM, CDE – Dr. Gavin is among the most respected doctors in the land, and it'll be interesting to hear his take on this – he's also recently been named to Amylin's board of directors and like the Lilly symposium, this should be enormously interesting as we start to think more about insulin being introduced *later* due to new incretins but earlier just due to a more aggressive approach. Finally, Lawrence Blonde, MD, FACP, FACE, Stuart T. Haines, PharmD, BCPS, BC-ADM , and John (Jack) Leahy, MD will speak at Merck's symposium entitled, "A Multidisciplinary Approach in Addressing Novel Mechanisms in the Management of Type 2 Diabetes." This symposium hopes to provide a broader understanding of type 2 diabetes pathophysiology, particularly focusing on the contribution of incretin abnormalities. The program will describe present and future therapies that address incretin abnormalities, focusing on DPP-IV inhibitors, likely Januvia in particular.

The symposia continue later on Wednesday afternoon with Dana Armstrong and Allen B. King's talk on "The Art and Science of Insulin Pump Dosing Self-Management Formulas." Dr. Thomas A. Buchanan, Dr. Robert R. Henry, and Virginia Valentine will also examine the evidence behind whether there is an intrinsic vascular benefit to TZDs, sponsored by Takeda Pharmaceuticals. In addition, the Amylin-Lilly Alliance will be presenting a Clinical Case Challenge: "Measuring the Benefits of Integrating Incretin Mimetics into Management of Type 2 Diabetes," presented by Donna Miller, Dr. Anne L. Peters, Laura Want, and Catherine L. Martin.

Thursday promises to be equally exciting, with several sessions of note. The day will start with an introduction to inhaled insulin and Exubera – we hope to learn more about launch, what's required in terms of pulmonary lung testing, what equipment is being made available to doctors, what incentives there are for patients to sign up, etc. Later in the morning, Dr. Lynda K. Fisher will be discussing the use of insulin pumps in children and adolescents – she works with Dr. Fran Kaufman at UC Children's - we never fail to

learn enormously from either. In the early afternoon, Peggy B. Bourgeois and Charlene K. Postigo will be giving a reimbursement update, and Carol S. Manchester will be talking about glycemic management in acute care. Later in the day, Mary Halvorson and Dr. Francine Kaufman will be talking about intensive management of type 1 in children while the "AADE Outcomes System: Implementation/Evaluation" will be presented by AADE President Malinda M. Peeples, Janice Lynn Koshinsky, Janis R. McWilliams, Mark M. Peyrot, Linda M. Siminerio, and Janice C. Zgibor. The second day of the conference concludes with several interesting sessions. Karen M. Green and Janet Regan Klich will be discussing pump therapy in the outpatient session, while Donna L. Martin and Linda H. Vogt will focus on improving inpatient blood glucose control. Also of note, Mary Beth Modic and Rebecca Sauvey will be discussing the implementation of glycemic protocols, and Mary M. Austin will be talking about patterns for success in blood glucose monitoring.

Friday will start with a session entitled, "GLP-1 and Amylin: Exploring Hormonal Actions" – this is a not-to-be-missed. Top educator Gary Schneider will then present data on continuous glucose monitoring. Later in the morning, Dr. Francine Kaufman will lead a breakout session on the epidemic of type 2 in children and youth. The afternoon should feature several interesting sessions as well. Nancy D'Hondt will give a talk entitled, "2006: A Drug Odyssey," while Judith Vance and Donna Zazworsky will discuss establishing diabetes self-management in primary care – we're fascinated by this one, since primary care is where so many problems start. In addition, Marcia Draheim will talk about technology use in diabetes education and Judith Barkanic and Christine Gilhool will discuss the approach to diabetes and pregnancy management. The third day of the conference will conclude with a session on management of hyperglycemia in the hospital presented by Dr. Etie Moghissi and a session entitled "Current Diabetes Landscape: Reassessing Strategies/Attitudes" by Dr. William Cefalu – we don't want to miss this last one since Cefalu has written some profound words on this subject.

On Saturday, the final day of the conference, Norbert Knack will present on "The Quest for Euglycemia in Cardiothoracic Surgery." Later in the morning, Dr. Daniel Lace will discuss Medicare Part D and diabetes education, and Nathan Painter will talk about new and standard treatment options for type 2. Finally, Judith Campsey and Susan Pettit will discuss prediabetes and metabolic syndrome.

And remember, these are just our top picks – there are many more interesting sessions as well!

–Kelly L. Close

2. **DCU Interviews 2006 ADA Educator of the Year Geralyn Spollett on the State of the State – Diabetes Care Today**

Geralyn Spollett is known as educator extraordinaire – she is the stuff of which legends are made. Giving her cell and home telephone numbers to patients, some of whom call her in the middle of their night when their insulin pump fails, is all in a day's work for her, days that last 24/7. Her commitment is just one reason why ADA named her Diabetes Educator of the Year this year – an enormous honor. She is the Associate Director and Adult Nurse Practitioner at the Yale Diabetes Center, and she spoke to us about her 27-year career.

Kelly: Thanks so much for speaking with us today! You've had an incredible career that is admired so greatly in the industry and among your peers; maybe you can start by telling us how you got into diabetes care?

Geri: I started at the Joslin Diabetes Center in 1978. Basically, I went to Joslin because I had worked at a hospital in Boston, and I realized that by the time that we saw many diabetes patients as inpatients, it was impossible to improve their care because they already had so many complications. Many of them just weren't taking good care of themselves because they had not had the education necessary to do so. So I felt I would rather be on the other end of the spectrum.

Kelly: You've been described as having a diabetes heart, because you've treated people with diabetes in street clinics for the indigent and homeless as well as in some of the most affluent cities in the country. But many are worried that not enough people are going into diabetes because of difficulties with reimbursement and just difficulties in training. I wondered if you could talk about your view on people going into the field right now.

Geri: I'm definitely worried. We have probably 26,000 people in the country who are trained as diabetes educators. In terms of certified diabetes educators, we're up to between 13 and 14,000, according to the NCBDE. But the anticipated number of people with diabetes is going to far exceed that. We're talking about maybe as many as 41 million by the year 2025. That's the CDC estimate. That includes people with pre-diabetes or metabolic syndrome. These 41 million are going to need qualified care. So clearly there are two avenues to this. One is that we need to be educating primary care practitioners to take care of people with diabetes in a much more aggressive way. They feel very uncomfortable with all of the technology that's come about in the last four or five years and will be continuing to come out in the next four to five years. We also need to recruit more people who are interested in taking care of people with diabetes and educate them so that they are either teaching primary care or they are accessible to primary care either through some kind of private contract system or community service system or public health system that allows access to CDEs. I think that right now that's one of the biggest problems – most CDEs are somehow connected with endocrinology or hospitals, so unless you get into that system, it's impossible to access that care.

Jim: You've said that you're just a phone call away from your patients, but you actually don't get paid for those phone calls, I believe. Is that a failure of the reimbursement system?

Geri: I think it is. The other problem is that it's so hard to get some of the reimbursement even for the face–to-face consultations. Not for me because I'm a nurse practitioner, so I bill under nurse practitioner codes and include education in the management. So I don't have a problem, but for the system at large, there are still problems. You have to have the right documentation. You have to be careful that you get the right referrals from certain insurers that cover diabetes education. And then the number of visits can be limited. So the whole telephone business and trying to get reimbursed for that – it's very difficult. I do send e-mails back and forth with my patients. As a matter of fact, what I'll tell them is, "Phone me if it's an emergency. If it's not, e-mail me. If it's a question, I promise I'll get back to you within 24 to 48 hours." And I do that. Some of that happens at ten o'clock at night, but it happens. That's what I have to do. I don't know how to say this and not sound like a martyr because I really don't feel like a martyr. This is what I do. This is what I love. If I can help somebody, I'm glad to do it. It doesn't matter to me if it's ten o'clock at night. My children are grown now, but they always understood that the job that I had was important.

Kelly: What could happen on the policy front so that people might be a little bit more interested or a little bit more able to go into the field? This is both a problem on the nurse and the physician front. As a patient, I wonder who's going to take care of us 10 years from now?

Geri: Well, I don't think the crisis comes ten years from now. I think it's going to take a little bit longer. In fact, I think it's a policy issue, but I also think that it's a financial issue. One of the things that I have talked about is the fact that most other specialties have different kinds of procedures that they're allowed to charge higher rates for. For instance, a gastroenterologist can do upper GIs, lower GIs – you know, they spend a day in the hospital doing all kinds of invasive procedures and testing. And they can charge a hundreds of dollars every time they do a colonoscopy. When you work in endocrine, since you're working with hormonal issues, it's more diagnosis and treatment with blood tests, and on the diabetes side, invasive procedures are relatively limited. Most of the things that we ask for are exercise stress tests, cardiology issues, eye problems, neurology work ups. They are all done by the various sub-specialties. And whatever testing they do, they take the reimbursement or coverage money. So the fact that we feed all of these specialties with the needs of people with diabetes doesn't offer us any kind of kickback. You know, it sounds funny to say that, but if you look at the process of taking care of people with diabetes, most of those costs are not directly endocrinology costs. They're not the cost of the visit for the endocrinologist. They're not the phone call costs. It's all the other complications, which are much more costly to take care of.

Jim: What sort of proposals would you make to change the reimbursement system? Is it a matter of going to the insurers, to government, to Medicare and trying to convince them about the value of what educators do?

Geri: I think it's that, but also I think that at some point there has to be separation in practices between educators and endocrinologists. CDEs need to become more accessible outside of the

endocrinology office. And once they become more accessible they will get into other systems that aren't completely diabetes dependent or focused. I'm in a center with five doctors. I'm the only CDE nurse practitioner. And that's because we can't afford another CDE nurse practitioner based on what our reimbursements are. At one point, my reimbursement rates for Medicaid were $10.53 per visit. Honestly, that didn't even pay for the paperwork and the processing through the hospital billing system.

Jim: But doesn't that speak to the problem that the payers – public and private – don't recognize the value of the work that not only you do, but that the endocrinologists do?

Geri: Absolutely.

Jim: So how do we break that impasse?

Geri: I wish I had the best answer for you, but I only have a couple of answers that are probably not the best because they require time. The problem with Washington – now you're going to here my cynical side – is that Washington is not really interested in access and availability of health care because healthcare as a business has such a big lobby. Politicians are interested in satisfying the people who put them back into their positions. That means the insurers, and it means people who pay the re-election costs. It's not the patients. They're not listening to the patients. I think that it's ridiculous that we don't have some kind of national health care system that's not Medicare/Medicaid to take care of people who have multiple issues. When we're fighting to get reimbursed for ourselves, as CDEs, in some ways we're perpetuating the system that's built on a shaky foundation to begin with and encouraging a private pay rather than a national health system.

Kelly: Are you surprised that diabetes has not captured more of the public's attention? That we don't have public health advocates ringing the bell about how 4,000 Americans each day now are estimated to be diagnosed with it? Why haven't more people been made aware of the crisis?

Geri: Because diabetes is not new. And because diabetes is not life-threatening in the same way that HIV/AIDS was life-threatening and new. Diabetes, as you know, is an ancient disease. It goes back to the Greeks. I remember as a little girl, my grandmother had a friend who "had sugar." When she came, my grandmother didn't make any dessert. So, in the back of our minds, we've all known somebody who had diabetes and they've lived and it wasn't something that was going to strike them down today. I also think that we've tried to tell people with diabetes that they can live long and healthy lives. I think that's a positive message, but it is also somewhat of a contradictory message. On the one hand, we're saying, "It's not so bad," but on the other hand, it's very bad. Take the mask off diabetes and say, "Look, this is a killer disease. Look how many people die from heart disease related to diabetes. Look how many people have blindness related to diabetes. Look how many people have kidney disease related to diabetes. Look at how much federal money is spent on taking care of patients with diabetes." We just don't want to face it. Even the ADA for years would not use any kind of terms that sounded like "scare tactics" to talk about diabetes because they felt that it was disabling to the population with the disease. And so we've spent a long time noodling and doodling around diabetes to make it more acceptable to the people who have it, which I think in turn has come back to slap us in the face when we talk about it as a serious disease.

Jim: You've done a lot of in-patient work. Are you seeing more people in the hospital who are getting heart disease and so forth at a younger age? Do you think that will make a difference in terms of people's awareness?

Geri: No, I think what's going to make a difference is the type 2 among children. I think that there are more people who are sitting up and taking notice that these kids are going to be our next health care crisis in diabetes. If you have a little kid at age eleven who is overweight, who has high cholesterol and diabetes – what is this kid going to look like 20 years down the road when they're supposedly at the height of their productivity?

Kelly: Do you think that our diet is continuing to get worse or do you think some of the public service campaigns are working?

Geri: I don't see any change at all. I'm always amazed when I take a history and somebody tells me they eat no fruits or vegetables. I mean, none. Everything comes out of a box. They eat a microwave breakfast, and they have a grilled cheese for lunch, and they have hot dogs and not even beans. I

think it's hard unless you have somebody who is really pushing and really takes the lead and becomes very adamant about it by saying, “We're going to change our family diet, and we're going to eat differently. It isn't going to be a pick-up meal.” That requires a lot of things. First is money to buy those foods. Second, it also requires somebody in the household who is going to be responsible for cooking and planning those meals. Third, it requires that the household be able to at least eat together at a similar time. I don't necessarily mean sitting down at a table, but that there is a meal time when people can come, make a plate, and sit down and eat. One of the things I ask is – do you eat with your family? No. Well, why not? Well, so-and-so has this plan, and so-and-so has that.

Jim: And the lack of a family structure produces poor eating habits?

Geri: Let me describe a family to you. This is not atypical. Mom is head of household. The male figure in the family may or may not be the dad. Three kids. Two teenagers, one younger kid. A teenager has a girlfriend or boyfriend who may or may not be part of the household. There may or may not be a young infant in the household. Younger kid is sort of ignored because of the stress of the family with the two teenaged kids. Mom works as a certified nursing assistant in a convalescent home. They're not in any kind of position where they're really getting many benefits. They work off shifts. So their schedule may be very different. They come in and they cook the food. If the kids eat, they eat. If they don't eat, they don't eat. If they want something else, it's got to be fast and easy to make, but they try to also include traditional foods. So what ends up on the stove is a big pot of rice and beans and then sometimes they have meat, sometimes they don't have meat. But there's no fruit or vegetables. Mom is completely overwhelmed by trying to provide care for these kids as well as provide physical and emotional and financial support. If there's a male figure in the household, they may or may not be contributing to the family. When you think about how these people live day to day and what their schedules are, it's alarming. Then you add diabetes on top of it. The biggest question I have for my patients is, "Did you take your insulin today?" Because whatever is going on distracts them from their own self-care, even something as basic as taking their insulin.

Kelly: So given that scenario, what do you think about when you see the newer therapies or medical devices that are more complicated and more expensive? How practical or relevant are these new therapies for the population that you just described?

Geri: Let's talk about Byetta for a minute. Medicaid covers Byetta, so that's not a problem. And because it's in a pen and easily injected, it isn't a problem in terms of actual delivery. The issue is getting patients to take Byetta before they eat a meal, the timing as well as describing to them what constitutes a meal. With continuous glucose monitoring, if I plug them into a monitor and they return in three days, and I download the data and show them what the issues are. So, they don't have to do anything except protect the device when they take a shower. In terms of insulin pumps, things get a little more complicated. If the patient has Medicare/Medicaid, I have to prove that the person has type 1 diabetes. It’s more of an issue with type 2 because Medicare doesn't cover type 2 right now. So that's a bit of a problem. If they have private insurance, then it’s not an issue.

Jim: What's your experience with getting patients to test their blood sugar at home?

Geri: I think patients will test if they understand what they're testing for. If you give them a machine, and you say to them, "I want you to test your blood sugar four times a day. Write it down and come back to me," then they won't do it. I wouldn't do it. You didn't explain why they have to do it and it’s a big pain. It hurts. It's expensive. Forget it. So I'll say to my patients, "Look. We just started this therapy, whatever it is." Let's say we put them on pills. "I need to know that the pills took care of your blood sugar during the night so when you woke up your blood sugar was in this range." I write down the numbers for them so they know what we're talking about. "Because if your blood sugar is better when you start the day, then the chances are, with good eating, you're going to stay okay during the day. So I need to know what your fasting blood sugar is. The other blood sugar I want to know is either before you eat dinner or after you eat dinner and here is the reason: If it's before you eat dinner, then I can tell what's going to happen when you eat your biggest meal – if your blood sugar was at target or if your blood sugar was out of range. And vice versa for two hours after the meal. If you tested before you ate your food, then two hours after the meal you should be in this range. And so that's why I want you to test. You only have to do it for a

week. At the end of the week, either e-mail it to me or drop it off at the clinic (because many of them live in the neighborhood around the clinic), and then when I see you in a week, we'll know what to do.

Jim: We have a shortage of diabetes educators, so how can we get more professionals to enter the field?

Geri: This is a great career, but in order to do that, we -- diabetes professionals -- have to create tracks for these people to get educated…We have to start talking about the fact that this is a great way to practice health care and that taking care of people with diabetes is not boring. On the contrary, it's very exciting; it touches our entire health care system -- you have to know human nature and you have to know the physical body and you have to be in touch with the emotional/spiritual side in order to provide good care. And so it's a very fulfilling role. It's not 9-to-5, turn a few buttons, and go buy a meter. I'm very passionate about this. And so when I talk about it, I talk about it with that kind of passion because I believe in it. We have to try to get people to look at it in a new and different light, so that they realize that this isn't a boring, "check the numbers, take your insulin, and good-bye, buddy" type of job. It really is something that involves a more holistic, open dialogue among patient and provider where no one really has the answer, so you're working together.

Kelly: Is there any parting advice that you would have for patients that we could give them?

Geri: Oh, boy. There are a couple of things that I think about. I have to share this with you. One of my patients who works very hard at his diabetes was working as an umpire for a little league game. He was checking his blood sugar and eating and doing all of the things that he normally does to keep his blood sugar where he wanted it during the game. And then on a very hot day, he passed out because his blood sugar went down into the 30s. It caused quite a stir. They had to get the ambulance; the kids got all worked up. And what he said to me was very profound. He said, "You know, my victories are always private, and my defeats tend to be public." There hasn't been a day that's gone by that I haven't thought of that and what that means. I mean, when you hit target and you're having a good day, nobody's patting you on the back and saying, "Good work," because that's what's expected. But when you have a day where things don't go well, despite your best efforts, everybody seems to know. And so I told him, "I hear you and I'm sorry. Because you're right. So, this is what you need to do. You have to share the good news because otherwise, nobody's going to know about the good news since we tend to keep that to ourselves. So when you're doing well, you need to say to somebody, 'You know, I made some great decisions today and I've managed to keep my blood sugar exactly where I wanted it to be and I'm feeling really good about that.'…And your friends will rejoice with you; they'll understand and they'll listen. The people who don't listen don't matter anyway."

Kelly: Wow, thank you so much for such a note to end on …

—Kelly L. Close and James S. Hirsch

3. DCU Interviews Former AADE Dr. Jane President Kadohiro on Policy, Reimbursement, and More…

Fifty-one years ago, Jane Kadohiro was diagnosed with type 1 diabetes, but education allowed her to manage her disease and inspired her career. She has devoted much of her professional life to diabetes, including serving as president of the AADE in 2002 and 2003. Dr. Kadohiro recently spoke to Kelly Close and Jim Hirsch about how diabetes care has changed and the biggest challenges faced by patients.

Jim: When we get a chance to talk to someone who has been involved in the diabetes world for as long as you have, it's always useful to get some historical context about how diabetes education – and for that matter, how diabetes care – has evolved over the years . Maybe you can reflect on what you think some of the significant changes have been.

Jane: Wow, that's a loaded question. I've lived with diabetes almost my entire life – 51 years now. So to look at it from that perspective, I can think back to the time when education wasn't even really spoken about very much, except in a couple of areas of the country. Joslin was one center, and Children's Hospital in Pittsburgh goes way back as well. I was diagnosed in Pittsburgh, so my family most certainly benefited from that. We rarely called it diabetes education back then. We

didn't refer to people who talked to us and gave us information as diabetes educators, but they were definitely there.

Jim: Why wasn't education more talked about?

Jane: I think for a couple reasons. For one thing, nurses, dietitians, and pharmacists are the primary professionals who serve as diabetes educators and their roles were much less expansive than they are now. They basically followed orders given by somebody else. Pharmacists just doled out drugs. But their roles have changed a lot into more independent practice, into certainly more of a solid profession. And other disciplines have become increasingly important members of the diabetes education team.

Kelly: Do you think it changed because of the recognition of the role that these individuals can play or because we realize that the women who invest in these careers can do more?

Jane: Probably a little of both. I think that professionals realize that people with diabetes needed information. It's also that in the past, patients just didn't get much information, period. For instance, it's only in the last 15 to 20 years where they'll actually give you your blood pressure reading when you're in a doctor's office. And home monitoring was in its infancy and rarely used.

Kelly: What about the reimbursement environment? To this day, diabetes education isn't reimbursed as well as other areas of care. Why do you think that area has been so slow?

Jane: Diabetes education really falls into the role of prevention. And prevention has never been given much attention. Certainly it's given lip service, but only 1 to 3% of U.S. health care dollars are spent on prevention. The rest is spent on care. And most of that money is spent for tertiary care toward the end of life: emergency, ICU… so that plays into it right there. Then, we don't have the evidence. We're working on that, and we're gaining a little bit of evidence.

I use the term "diabetes education" carefully because it's really diabetes self-management training we're discussing; I like to call it "therapy" because we're not just telling people what to do, which is what a lot of people interpret as education. In fact, that's only about 10% of what an educator does. What patients really need on top of the facts is somebody who can work with them to assist in figuring what the barriers are for them in doing the things that science has shown us are critical. The CDE is really asking the patient, "What are your goals for yourself? How can we fit this into your lifestyle? And where can we start and then move forward?" rather than, "Here are 17 things you need to do tomorrow. Go home and do it."

Kelly: Obviously a lot has not gone right in diabetes care. Two thirds of people with diabetes are not under control. Where are the main problems?

Jane: Certainly a lot of the main challenges are related to the AADE-7 Self-Care Behaviors [Healthy Eating, Being Active, Monitoring, Taking Medication, Problem Solving, Healthy Coping, and Reducing Risks]. It's hard to even pull out any one in particular. Food is a huge issue in our society. Are people able to set goals and follow those goals for their eating habits? They may want to set a goal that they will have five fruits and vegetables a day, and a goal eat three balanced meals a day. Are they able to take their medications as prescribed? For some people that's just plain difficult because of the cost of medications. Then there's the way that writing prescriptions and filling prescriptions is done. If I can't get to my pharmacy in that little window of time in which I can refill a prescription, I may have to go without my medications for a couple of days. But I have a demanding job, the pharmacy closes at 5 pm, and I have kids to take care of. Well, it's all those life things that make it a real challenge.

Jim: What's also discouraging is that the medical devices, the drugs, and our knowledge of diabetes are all getting better, but the outcomes are not getting better and by some measures, they're getting worse. Why is that?

Jane: But are patients really working with an educator to figure out how to best fit all of the new therapeutics into their lifestyle? Most of them are not.

Jim: So while the products are good, they're only as good as your ability to actually use them.

Jane: Exactly. To make an analogy, I am not a computer geek. In fact, I am pretty bad. But, I have a really good computer at my office. I've got far more programs on it than I will ever be able use. But if I don't have somebody here coaching me – not just teaching me once when I go to a class,

but actually here on site that I can call up *now* and say, "Oh, I'm stuck. I did something wrong and I lost something" - then I'm not going to get my product out. I like to compare the situation for diabetes patients and new diabetes therapeutics to that.

Kelly: To extend that further, some people just don't want to be bothered with the computer beyond Word and Excel. Would you say that there are some patients who just don't want to be bothered because hyperglycemia by and large isn't painful, or because they don't have the resources, or is it somewhere in the middle?

Jane: I think it's all of the above. I think there is a population of people out there who would go to a diabetes educator if they were referred to one, even if they had to pay out of pocket. But they aren't offered that opportunity. And then there are others who just don't have the money or don't feel that they need the education. Some patients are extremely self-motivated and are able to figure all these things out for themselves.

Kelly: What percentage do you think that is roughly?

Jane: Probably less than 10%. That's being generous. By far, most patients benefit tremendously from working with a diabetes educator.

Jim: There's been a lot of attention on pay-for-performance programs that operate on the idea that the only way that you're going to motivate providers is by giving them a financial incentive to produce better outcomes. What's your feeling about that?

Jane: I think that's a real challenge for the whole system. There are a lot of good points to it – however, is it really fair for a provider to not get paid when they've got a patient who is just not ready to learn yet?

Jim: So providers would be punished for trying to take care of the needy patients.

Jane: Right.

Kelly: Do you have any feelings about some of the new products and drugs and devices that are on the market now? What things are out there now that you like or don't like?

Jane: I am just astounded by the number of products and drugs that are out there now. It's tremendous. What is absolutely needed, again, is for the patient to automatically get the self-management training they need to use those products – to make adjustments based on blood sugar readings, or as their own day-to-day activity changes. If the patient does not learn how to use these products in the context of what's happening each day in their lives, then they won't use these products as they were intended, and they're not going to get the outcomes that they need.

Jim: The burden is on the patient to make the adjustments - that hasn't changed since insulin was discovered in 1922. So, why has the system resisted creating a structure that generously funds educators to teach patients how to make those adjustments when that has been the challenge for 80 plus years now?

Jane: I could be a little bit of a skeptic here and say, "Do some people in the system and some providers feel that if patients become too able to self-manage, then that is going to affect business?" I don't think that's where most people are coming from, but certainly there are some providers out there who might feel that way.

Kelly: Let's talk about the payers for a moment. In all your years, you must have sat down with an insurance company and explained the situation to them. What has their response been?

Jane: The CEO of the insurance company or the health plan is there for today's bottom line. And, if at the end of the year when they close their books, their bottom line is not improving, they may not have a job in another year or two. But when they put resources into prevention, they are not going to get an immediate payoff. The payoff comes in three or four years. Some studies have actually shown that you can at least start breaking even in two years by covering all of the preventive activities. But the CEO is worried about the bottom line this year.

Kelly: How do we break that impasse?

Jane: I think that it requires gathering all of the payers together. Because one of the other arguments from payers against prevention is that the company (their client) may switch to a different health plan next year so the patient the payer had covered for prevention is now going with a competitor..

Patients switch health plans all the time. Payors are asking, why should they put money into prevention when somebody else's health plan is going to benefit from it?

Kelly: What about the potential for industry? Is industry devoting enough resources in terms of education, and how could you see that changing?

Jane: I think that varies quite a bit. A number of companies hire well-seasoned educators to work with educators as well as physicians in their communities. I think some of the pharma regulations have probably increased the role of educators as their sales forces are more limited in what they can do.

Kelly: Right, in terms of sponsored travel, etc. No more golf outings!

Jane: Exactly. It's far more restrictive than in the past!

Kelly: Do you have any particularly good examples of industry's increasing use of educators?? I know that certainly Lilly, J&J, and Abbott have well-regarded programs. Are there any companies in particular that you can point to that you think have done a great job in recent years on this front?

Jane: I think the ones you've mentioned. Certainly Amylin has brought quite a number of educators on board to start working with the health professional community to get their product out. Novo Nordisk has increased the things they're doing, as has Pfizer .. quite a number.

Kelly: How are you thinking about diabetes prevention, broadly?

Jane: The tricky thing with prevention is that it's not a one-shot deal, and so I think we all need to be careful that we're not selling what we do as educators as just, "Come to our class, and let us tell you what you need to know and help you get started, and then drop you." It's about being a coach forever; we have to be there to be on call, be there to recharge your batteries when your batteries are starting to run low with frustration or whatever.

Kelly: Right. What about your perspective as a patient - could talk about what's helped you personally?

Jane: My parents never told me there was anything I couldn't do. They sometimes got criticized by their friends – "You're going to let her do that?" I went to Europe when I was 20 and in college, and my parents just got chastised by their friends. But if you grow up with the knowledge, the self management ability, the support of family and friends, and a "can do" attitude, then you see diabetes as maybe a little bit of a challenge, but it's not going to hold you back or handicap you. I have been so blessed with so many wonderful life experiences and a wonderful family and friends!

Jim: I wonder what you think about some of the changes that have happened in making diabetes a little bit more mainstream – the mass communications about it and so forth.

Jane: I think it's a really good thing. People who don't have diabetes have a lot more appreciation for it now. It's becoming a household word. I know early on, I could not get the media to do anything with it because it was boring. There was nothing sexy about it. And now everywhere you turn, you're hearing about diabetes. I think in some ways the ability for companies to advertise their drugs and products – consumer advertising – has made a difference.

Jim: Would you have any advice for those companies?

Jane: Yes, they should close the ad with a powerful statement: "Get this product and see a diabetes educator!"

Kelly: I know that you did a lot of national and international speaking during your tenure as president. Are there any models that we should look at from the U.S. perspective?

Jane: Certainly, some of the European countries have done quite a lot; the UK and Scandinavian countries, for example. I think what sets US diabetes educators apart from educators in other countries is that we come from more than one discipline. In a number of countries, there are diabetes nurse specialists, which is great, but we have been more inclusive since the beginning, with behaviorists, social workers, and a number of other disciplines.

Kelly: How are CDE programs reimbursed or covered in other countries?

Jane: A lot of countries have socialized medicine, so it's partially covered by that. Other countries will cover children until they're adults, and then a new system takes over.

Kelly: Do you think we should be getting increasingly optimistic or pessimistic? For example, we just talked to a fairly well-known diabetes clinician in the UK, who was doing a trial, and he said that he was very excited because he was working on a two-year randomized controlled multi-center

trial focusing on urine versus blood glucose monitoring. That struck us as very backward, but he basically said that he wants to be on the podium at EASD in a couple of years talking about this trial. I mean, you hear about stuff like this and you just shake your head. I think it's hard to be optimistic.

Jane: It's hard to be optimistic, but as a young professional I would get so frustrated with the media not paying any attention to my organization, the department of health. They would say, "You don't need an epidemiologist on staff, you don't need to worry about outcomes, you don't need blah blah blah." And so this many years later, you look back and you say, okay, the seeds are planted and I never stopped talking about it. But nobody listened. Little by little, others came around and eventually listened to somebody else somewhere. I believe that persistence pays and that if you live long enough you may see some of your hopes and dreams come true- and it doesn't matter who gets the credit!

Kelly: Do you believe we're making any progress on the childhood obesity front?

Jane: I think when you look at obesity you've got to really work with the kids, the schools, the families, and the communities. It's a huge public health issue. We thought tobacco control was hard. How are you going to change all the fast-food offerings? How are you going to change restaurants and markets? It's a tremendous challenge.

Kelly: We were at the Children with Diabetes conference in Orlando, and at Sea World we saw that some of the restaurants actually had nutritional information. That was a start … would you say you're optimistic on the obesity front?

Jane: With caution. It goes back to the, " …so we know it, but now are we going to do something about it?" And it's the same with reading labels. Years ago, I was fighting to get sodium listed on labels for the hypertension program here. We've come a long way.

Jim: So do you believe it's reasonable to think that we would see more and better nutritional information on labels and start to see it in restaurants?

Jane: I'm sure we're going to see additional information. But are people going to use it so that it improves their health?

Jim: When you were president of AADE, did you meet with many political leaders? With the prevalence of the disease, people in these positions must have been affected by it personally or through family or friends. You have to wonder, where is the FDR for diabetes?

Jane: We've actually had a number of good supporters on the hill and with other diabetes as well as governmental organizations. The Diabetes Caucus continues to attract new members. But money is on everyone's mind. Another sad truth–and I hate to hear myself say this – there are a number of people who really feel that people with diabetes got it because they deserve it. " …If you didn't let yourself get overweight, if you lived healthier… You didn't need to have this, so why should we pay for your lack of discipline?"

Jim: Even though obesity is much more complicated.

Jane: Yes. There's a physician out of Yale's School of Medicine and Public Health, Dr. David Katz, who talks about the work of the food industry in adding sugar and salt to our food. When I was a child, you didn't find cereal, dry cereals, with sugar and salt already in them. You didn't find a lot of those products in bread or anything. But almost everything you eat now has salt and sugar in it. I didn't realize this subtlety until I heard him speak - those products affect the hypothalamus, which controls the appetite, so when you eat more salt and sugar you become more hungry and eat more. Really sad! Our portion sizes … super sizes are the way of life in our country. The obesity epidemic is most certainly another arena in which diabetes educators can make a tremendous diabetes difference!

Kelly: Well, we're delighted to be able to bring our readers some of your thoughts, especially since you have been such a fixture at AADE, but won't be at there this year … but we'll send everyone your very best and will look forward to seeing you there next year!

—Kelly L. Close and James S. Hirsch

4. Spotlight on Obesity: Thoughts from ADA & ASBS

While we focus most of our energy on diabetes, we are increasingly concerned about its connection to obesity. In our last newsletter, we wrote about Byetta as the darling of the ADA conference. But what was the buzz really all about? Certainly, Byetta improves blood sugar levels, potentially postpones insulin use, and perhaps even reduces the number of other oral medications required. But that's not what doctors and CDEs want to tell you first. Everyone wants to talk about Byetta helping diabetics lose weight. Sometimes lots of weight. While the clinical trials for Byetta showed about an 8-pound loss at the 10 mcg BID dose, in practice patients are frequently losing much more. Anecdotally, we hear of people losing several times the amount of what subjects lost in the trials. It was not uncommon to hear stories at ADA of 30, 40, even 50 pounds of weight loss.

To put this into perspective, we've heard that in a population of obese people, about 20 percent will be type 2 diabetics. But in a population of type 2 diabetics, about 80 percent will be obese. So for type 2s, losing or controlling body weight can be crucial in managing their diabetes. From our conversations with obesity experts, we know that multiple potential pathways exist for treating obesity, and we expect the most successful ones to involve a combination of therapies. Despite the hype, for the first time in many years, we left ADA feeling that potentially promising obesity treatments are being developed.

Endocannabinoids still hold promise, though enthusiasm has waned

Byetta is not alone. The ADA had many presentations, posters, exhibitors, and sessions dedicated to helping type 2's lose weight. We attended sessions about the emerging class of endocannabinoids, lead by Sanofi's rimonabant (Acomplia[2]), which Sanofi-Aventis management still hopes to launch in the US by year end. Sanofi's management team noted on its Q206 earnings call that it had no reason to believe a panel meeting would be required. We found this extremely surprising given the controversy around CNS with the drug. The breakthrough learning for researchers has been discovering that the body's metabolic pathway isn't only centrally controlled. Rather, there are peripheral hormonal systems in and around the gut that play crucial roles in regulating food behavior. This finding opens up wildly new ways to think about obesity. While rimonabant is promising – it's orally administered and caused trial subjects to lose 15 pounds or more – it also came with some potentially limiting side effects related to anxiety. Yes, it's not exactly termed a happy pill. We applauded the FDA's decision to approach with caution Sanofi-Aventis's rimonabant application, as the rates of depression in trials merit further inspection: in at least one trial, the drop-outs among those depressed were three times the average. The June 29 launch of Acomplia in the UK will generate more data on the drug (if anyone pays for it), and ultimately we anticipate that this class will be used in the US, though with careful monitoring, as rates of depression are already higher in the obese than the rest of the population.

Leptin recast in combination with amylin

Amylin, which understands the connection between weight-loss pharmaceuticals and money, has multiple potential obesity treatments in its pipeline. At ADA, we attended an inspired presentation hosted by Amylin featuring a discussion of that pipeline. Dr. Alain Baron, Senior Vice President of Research, discussed Amylin's approach to using its molecular franchise of neurohormones in obesity, reviewed animal data using amylin, PYY $_{3\text{-}36}$ and leptin for weight loss, and outlined potential therapies for treating obesity.

We saw early phase 2 data looking at the effect of current formulations of pramlintide (Symlin) on weight loss. Weight loss at 16 weeks for the 120 mg TID and 360 mg BID showed similar placebo corrected efficacy– 3.35% versus 3.25% respectively (n=38 and n=39 respectively). What was really intriguing was that in addition to experimenting in diet induced obese rats (DIO) with rat amylin solo, Amylin researchers decided to look at combinations of three molecular classes believed to influence some aspect of obesity – amylin, PYY3-36, and leptin. As background, we remind that leptin has been studied fairly extensively for many years because of believed potential for weight loss. Alas, seemingly to no avail. When Amylin combined rat amylin with leptin, researchers observed a synergistic effect on body weight in DIO rats –

[2] Acomplia had been bandied about as a trade name although once Sanofi received its approvable letter in February, there was suddenly zero mention of Acomplia (only rimonabant) on the website, in the press release, etc. Now, it's rather returned. Time will tell.

12% body weight loss with the combination compared to 6% with amylin and 2% with leptin alone. And, also exciting, is that the weight loss was specific to fat mass – lean mass was preserved. The study conducted paired feedings – and weight loss was not fully explained by the amylin effect of reducing food intake. Something else was going on. Dr. Baron noted that a likely explanation is that amylin was restoring sensitivity to leptin. We know that when fat mass decreases, leptin levels decrease. It is possible that amylin+leptin is "tricking" the brain. When Amylin combined all three neurohormones (Amylin, PYY and leptin), amazing things started to happen in these DIO rats. The rats lost almost 20% of their body weight – an outcome that approaches gastric bypass surgery weight loss results in rats! And, lean mass was still preserved. Only fat mass disappeared. Excellent.

In keeping with our theme of "combination therapy is the future," are we approaching an era of multiple promising pharmaceutical treatments for obesity that can be combined to achieve surgery-like weight loss results? Our belief was "yes," but we thought more investigation was in order.

While at the ADA, we strolled through the Bariatric Edge canopy within the J&J booth. Bariatric Edge is J&J's operating division within Ethicon-Endo (a division of J&J) focused on bariatric surgery. In addition to special tools for bariatric surgery – such as longer cannulas to enable better access in large bodies – in Europe, J&J has an adjustable gastric band for use in laparoscopic surgery for morbid obesity acquired through the acquisition of the Swiss firm, Obtech Medicalof in 2002. While trials are underway in the US, this division of JNJ is difficult to pin down. Even so, we would say the $110 million purchase of this Swiss company now looks pretty good.

Bariatric surgery on the rise with broadened CMS indications

We also signed up for the American Society for Bariatric Surgery (ASBS) annual meeting in San Francisco June 26 – July 1. In retrospect, we probably had misplaced expectations, anticipating too much from the wrong group of caregivers. This meeting was a gathering of surgeons who have a particular relationship with a patient over a relatively short time. It was not a gathering for clinicians focused on treating diabetes as part of a care continuum over a long period of time. We admittedly went to the conference looking for studies and presentations focused on describing the astounding result that over 70% of type 2 diabetics who undergo gastric bypass surgery experience a reversal of their disease! Put simply, we didn't find them. Granted, even at ADA, much of the discussion this year surrounded safety, but still…

The focus of this meeting was weight loss and achieving maximum weight loss with maximum safety. Reversing diabetes, hypertension, and hypercholesterolemia was a noted sidebar but definitely not the main event and not very well documented. The meeting fell short in other ways. Where we found ample evidence of emerging pharmaceutical therapies for obesity at the ADA (a diabetes meeting!) we found precious little discussion of emerging devices or new surgical approaches for treating obesity at the ASBS. We mostly heard discussions comparing safety and outcomes data for gastric bypass versus gastric banding – approaches that have been around for decades. Gastric banding has been used in Europe since 1987 but was not approved in the US until 2001. No "hot" sessions discussing devices that can be inserted non-invasively in an outpatient setting. No peeks at implantable devices that don't require a rewiring of the GI system. No "new new thing" at all! At the poster sessions, we finally got to ask one lone presenter what devices or products she was most excited about for helping her patients lose weight. Her response? Byetta.

Still hopeful, we turned to the exhibit hall in search of some buzz. Jackpot. We found what we'd been looking for. Or so we thought. The energy in the hall at Moscone West was palpable. We looked to Allergan/Inamed's booth thinking something new was happening with the LapBand (the only approved device in the US for gastric banding.) But all we saw was several bored sales people milling about. We looked straight ahead to JNJ's Bariatric Edge booth – no gastric band in sight by the way. Similar set of bored sales people biding time.

We looked left to Tyco's booth and found our crowds. The booth was packed. The company had something the surgeons wanted. Finally, we found the "new thing." Sure, we were a little worried because we thought we might have missed something big in our pre-conference prep. We'd dismissed Tyco as a stalwart supplier of high-quality cutters, cauterizers, and staplers – not an innovator of bariatric surgery devices as yet unveiled. So we elbowed our way through the deep crowds and found the source of all the excitement: a

bank of 15 laptops…all with a live feed to the World Cup quarter-final match between Germany and Argentina.

While the news of the ASBS meeting was essentially that there is no news, the promise of bariatric surgery in obesity and diabetes remains enormous. Researchers are trying to understand how gastric bypass surgery can "cure" many type 2 diabetics instantaneously. They know that weight loss is not the trigger, since type 2 diabetes sometimes disappears even before patients are released from the hospital—certainly before substantial weight loss occurs. Some believe that the redirection of gut hormones is the key, as the effect is unique to gastric bypass and does not occur so quickly in gastric banding, where there is restriction but no rerouting or short-circuiting in the stomach. In gastric bypass surgery, many gut hormones, including ghrelin, CCK1, PPY, GLP-1, leptin, and others—change dramatically after the surgery, generating much of the positive effect on glycemic control. While the idea of a surgical "cure" for type 2 diabetes is intriguing, few long term studies exist, and we've collected a wide range of numbers on incidence and longevity of reversal.

—Cindy Glass and Kelly L. Close

5. Homing in on Alzheimer's Disease & TZDs: conversing with AD expert Dr. Geldmacher

"Disease convergence" is in the news – diabetes and cardiovascular disease, diabetes and inflammation, and now diabetes and Alzheimer's. In a NYT article on July 17, we learned about Alzheimer's "type 3" diabetes! No surprise that a media maelstrom ensued.

Recent studies are showing that tight control of glucose levels is necessary for physical as well as neurological health, and this may be even more important in the elderly. At the 10th International Alzheimer's Association conference in July in Madrid, Spain, researchers presented crucial findings that type 2 diabetes may increase the risk of Alzheimer's disease, which currently affects 4.5 million Americans. It turns out that the answer to combating Alzheimer's may lie in existing drug therapy for diabetes.

Large studies reveal that type 2 patients are twice as likely to develop Alzheimer's, as compared to healthy individuals controlled for age and sex. In fact, researchers from Sweden conducted a study on 1,173 people, age 75 and older, and found that even individuals with pre-diabetes were 70% more likely to develop Alzheimer's as compared to healthy individuals, also controlled for age and sex.

Among this elderly population with pre-diabetes, those with high blood pressure had the highest risk of developing Alzheimer's. This finding is leading some researchers to speculate that diabetes-induced cardiovascular complications are implicated in the onset of dementia, including compromised blood flow to the brain. Others are suggesting that high insulin levels in the brain may be contributing to amyloid plaque buildup, characteristic of Alzheimer's disease.

A study sponsored by Kaiser Permanente examined the health records of over 22,852 type 2 patients who were followed for a period of eight years. Researchers found that the risk of dementia greatly increased when A1c levels were over 10. Individuals with A1c levels between 10-11.9 had a 13% increase in risk for Alzheimer's, as compared to individuals with readings below 10. The risk increased to 24% among individuals who had A1c levels from 12 to 14.9. An astounding 83% risk for Alzheimer's was found among individuals with very poorly controlled A1c levels, reaching 15 or higher.

The diabetes drug class known as thiazolidinediones (TZDs) may be at the forefront of reducing the risk or progression of Alzheimer's. A recent study sponsored by GlaxoSmithKline looked at the effect of pioglitazone (Actos) and rosiglitazone (Avandia) on the incidence of Alzheimer's in a population of 142,328 patients in the Veterans Affairs health care system. In this cohort, there were 20% fewer cases of Alzheimer's among patients taking pioglitazone or rosiglitazone, as compared to patients taking only insulin. The same trend was observed among patients taking these TZDs when compared to those taking only metformin.

Dr. David Geldmacher is looking at the potential of TZDs as a potential therapy for Alzheimer's. A recent study, sponsored by the NIH and Takeda, used pioglitazone in 25 nondiabetics with mild symptoms of

Alzheimer's for 18 months to evaluate its safety and potential to slow the disease. This early work successfully established that pioglitazone is safe at maximum doses in non-diabetics, and his team will examine efficacy in a larger pivotal trial. While nondiabetics are the focus of his work, that work is closely related to the observation that diabetics taking TZDs were at lower risk for developing Alzheimer's than those taking insulin or metformin.

Dr. Geldmacher told us that he originally expected pioglitazone – which seems to have better brain penetration than rosiglitazone in animals – to be more efficacious than rosiglitazone; he now anticipates a TZD class effect given that the rosiglitazone data are similar to his findings on the effect of pioglitazone in Alzheimer's patients The similarity of the results suggests that the better brain penetration of pioglitazone is not required for TZD activity against Alzheimer's and, in fact, GSK recently described its phase 3 trial in 2,500 patients with an eye toward securing labeling rosiglitazone for use in Alzheimer's.

Dr. Geldmacher said that while the mechanism of action is unknown, the glitazones appear to have a preventative effect on progression to Alzheimer's. "Based on the proposed mechanisms of action—and frankly, we don't know how the medicine is working and whether it's working by one or more than one mechanism—there are reasons to believe that the drug may have prophylactic effects, that is, either to delay the onset or reduce the risk for Alzheimer's disease in people who take it," he said.

Clearly, the goal would be to establish the prophylactic benefits of TZDs in Alzheimer's. However, while Dr. Geldmacher said this drug class might have such preventative benefits, conducting the trial to show them could prove difficult because of the trial length, high numbers of patients required, and expense. That said, he admitted that if the glitazones showed activity in altering the course of Alzheimer's disease, off-label use would be widespread.

Dr. Geldmacher, while clearly enthusiastic about the potential for TZDs and Alzheimer's, did caution that this work is very early. If he had one criticism of the media coverage, it was that reports went too far too fast with early results hinting at a cure for Alzheimer's disease.

Our takeaway? On the more hopeful side, we are glad to see another spotlight on the type 2 epidemic. We already have potentially promising drugs (a new use for TZDs?), a drug pipeline that's filling, and a call from leading experts to treat type 2 and pre-diabetes earlier and more aggressively.

—Cindy Glass, Erin Kane, Rozina Ali, and Kelly L. Close

6. Children with Diabetes "Friends for Life" Conference update

Close Concerns headed cross-country last month to attend the Children with Diabetes (CWD) conference in Orlando, Florida, along with 2,000 others (half of whom were children, from two weeks to 18 years) from 43 states and 11 (!) countries. It was inspiring and now having been once, we know we'll never miss another one - it's a must-attend for any family with diabetes. Participants are committed to learning about the physiology and management of childhood diabetes, and they reap enormous benefits by going – it's a mini-ADA.

Jeff Hitchcock and Laura Billetdeaux are known today by many in the diabetes world for creating and leading CWD; Jeff started the organization in the mid 1990s, after his daughter, Marissa, was diagnosed. Laura joined Jeff in 1999 shortly after her son Sam was diagnosed at age 8. Their website (www.childrenwithdiabetes.com) and events are highly respected throughout the industry – and revered by families with diabetes as the go-to source for everything they could want – questions, introductions, expertise. The organization has five weekly newsletters; 18,000 people visit the site per day, and the organization holds 3-5 meetings per year, in addition to its national conference.

CWD, which began holding national conferences in 2000, takes care of everyone, from toddlers in childcare to notebook-wielding parents who want to hear the latest research news. At the meeting, we chatted with patients, learned concrete management skills from doctors, and attended the CWD banquet, where Dean Kamen and Al Mann, early pioneers in pump therapy, received awards. In one of the most

inspiring moments of the conference, Jeff Hitchcock invited all those in the room who wore insulin pumps to come to the front of the stage, and it took at least five minutes for everyone to congregate – what a feeling of thanks for what this technology has brought to people with diabetes. Kamen and Mann gave touching acceptance speeches to the beneficiaries of their work. Then, as an added bonus, American Idol star Kevin Covais, who also has type 1 diabetes, made a surprise appearance and performed a few numbers.

The sessions at CWD were excellent – there were 6-7 at any one time, with a strong emphasis on the practical (pumping, treating hypoglycemia, counting carbs). The conference attracts phenomenal leaders in the field – examples of talks included Best Practices Update (Dr. Nathaniel Clark), Meter Accuracy and Continuous Monitoring (Dr. Bill Clarke), Talking With Your Child About Diabetes (star RN Joe Solowiejczyk), Prevention and Treatment of Hypoglycemia (CDE Gary Scheiner), Pumping Basics (pump expert and CDE John Walsh – anyone with diabetes and an interest in pumps must pick up, by the way, his newest edition, with Ruth Roberts, of *Pumping Insulin*, just out), Heart Health Update (Dr. Bob Bulgarelli), Glucose: The Good, the Bad, and the Ugly (Kim Kelly), The Lollipop Brigade: Diabetes Management for Preschoolers (Dr. Fran Kaufman), Understanding the Ups and Downs of Blood Sugar (Dr. Irl Hirsch), NIH Research update (Dr. David Harlan), and Type 2 in Kids – An Update (Dr. Fran Kaufman).

In one talk, Dr. David Harlan of the NIH showed the grim state of cure research, noting how little we truly understand about the inner workings of the immune system. He discussed the new possibilities of prevention-based research work and posited that identifying who will likely get diabetes is the future of this research. Unfortunately, much of the prevention-based work far has been unsuccessful so far.

Dr. Harlan also introduced a topic that came up often at CWD: the possibility of salvaging insulin-producing cells even years after diagnosis. The preservation of some beta cell function in diabetic patients makes tight control much easier and in the future could lead to regeneration of beta cells. The big problem, however, is that the medications for beta cell protection that have been tested in trials have led to serious kidney toxicity problems. While investigating persistent insulin production is important, Dr. Harlan predicted it would be some time before the research benefits patients.

Dr. Irl Hirsch's sessions focused on maximizing the effectiveness of multiple daily injection (MDI) treatment regimens and on understanding the ups and downs of blood sugar. Although many patients at CWD wear pumps, Hirsch's talk on MDI was nonetheless informative, while the talk on understanding blood glucose was standing room only! There, he discussed a number of hot topics in the insulin research arena and gave the audience management tips as well. His presentation focused on the importance of reducing both overall glucose and glycemic variability, which is associated with oxidative stress. He discussed the possibility of using basal insulin on a twice a day regimen, given recent data that show that even 24-hour insulin loses much of its effectiveness after about 12-18 hours.

Dr. Hirsch introduced two major concepts in his session on blood glucose: insulin lag time and insulin on board. Lag time is the amount of time between giving the prandial insulin and eating the meal. The goal is to have insulin and glucose peak at the same time. Because even the fastest insulin formulations take longer to act than the body absorbs glucose, a lag time of at least 10 minutes between shot and meal is the minimum, and often lag times of 30 minutes are more ideal. Dr. Hirsch said that patients on MDI should experiment and monitor carefully to learn what lag times work best for them. Shoot-and-eat insulin medication definitely does not work as well as a lag-time influenced approach. With this in mind, we're more eager than ever to see more progress from Biovail on VRAI (very rapid acting insulin) – see last month's DCU for more information on this (our company update this month shows this company was recently funded – excellent news from our vantage point since we love the possibility of more exploration into whether there could be faster acting insulin used in our pens, pumps, and syringes today, and potentially tomorrow in artificial pancreas technology).

Back to Dr. Hirsch's standing-room-only presentation. Insulin on board (IOB) refers to the amount of insulin in a patient's system in the hours after injection. At three hours post injection a good 40% of insulin may still be in a patient's system. When patients treat themselves for a snack or a post-meal high or low, it's important to assess how much insulin might still be in their system because that will strongly influence the treatment needed. Ignoring IOB can lead to dangerous insulin stacking if a patient adds an injection

while previously administered insulin is still working. However, Dr. Hirsch reminded his audience that the actual glycemic trend always trumps IOB calculations, which is why frequent SMBG is so important, at least until CGM becomes more available and reliable. Still – one major advantage of pumps is that most pumps today do the math for users and tell them how much IOB they have.

Many of the sessions appealed to specific patient groups; a pregnancy workshop, for example, was led by Dr. Francine Kaufman and Miss America 1999 Nicole Johnson Baker and Kelly Close, your DCU editor. Baker and Close have type 1 and discussed how, with fantastic healthcare teams (they were both overseen by pregnancy expert Dr. Lois Jovanovic via email and phone, with help from superb local obstetric teams), they were able to have extremely good glucose control and a successful, uneventful pregnancy. Young women with diabetes are often anxious about pregnancy; this session reinforced the possibility of having healthy, happy babies while stressing the importance—and feasibility—of very tight control before and during pregnancy. In a separate session, Dr. Kaufman also introduced the term "double diabetes" in children. It describes a growing number of children who are diagnosed with type 1 diabetes and then who develop insulin resistance—the hallmark of type 2—in late childhood, usually as a result of weight gain. Treating these patients is difficult, and this medical phenomenon represents a frightening new frontier in childhood diabetes.

The science at CWD was compelling but not-to-be-outdone, for the entertainment was outstanding as well. The exhibition floor was entirely kid friendly: sno-cones from Novo Nordisk, face-painting from Sanofi, teddy bears from Cozmo, and t-shirt decorating at the Medtronic booth. These were as impressive as the booths at ADA – in what reminded us of the two-story Novo booth in Washington at ADA, Novo had not just sno-cones but ice sculpting at its booth – *ice sculpting* (www.childrenwithdiabetes.com/activities/orlando2006/report-photo4.htm)!

The growth of the CWD conferences speaks volumes for their ability to deliver what families want – information, fun, and friendship. We encourage any one with a child with diabetes to attend this event next year – save the date, July 11-15, Disney's Coronado Springs Resort.

—Aviva Gilbert, Jenny Jin, and Kelly L. Close

7. DCU Company Watch

- **Eli Lilly/Taisho – Another one bites the dust:** Taisho Pharmaceutical and Lilly announced August 7 the termination of their license agreement for TS-021, the Japanese drug maker's oral DPP-IV inhibitor for type 2 diabetes. Taisho gave Lilly exclusive rights to develop and market TS-021 everywhere except Japan and China in early July of 2005. The termination came because the drug did not meet Lilly's standards for pre-clinical study results. Lilly still has its partnership with Amylin but this continues to thin the crowd for Merck and Novartis. We doubt any issues with TS-021 were a class effect since they came so early in development.
- **GluMetrics—Eye on the ICU market: GluMetrics** announced in early August that it has raised $9 million in Series B financing for its product GluCath, a consumable catheter intended for use in hospital ICUs as a 48-hour real-time continuous glucose monitoring (CGM) device. Dream team Versant Ventures and Advanced Technology Ventures have invested in the company's first institutional fundraising round. GluCath uses a boronic acid-based polymeric material that lights up in the presence of glucose. We applaud more products intended for the inpatient market, since that area has such high need. Although interstitial fluid has been discussed for monitoring in the hospital, we believe that products using blood may suffer less from issues related to lag time, interference, etc. This financing comes on the heels of the August *Diabetes Care's* story on a consensus statement by ADA/AACE on the necessity of intensive glycemic control in inpatient care – finally! Intensive control requires intensive monitoring, so the ADA/AACE recommendations could greatly expand the market for inpatient CGM devices, though we still believe that JHACO will make the real difference, and we're still waiting for more news on when they will make inpatient monitoring part of the accreditation, not just certification, programs. At any rate, the competitive landscape here is extremely interesting, with Optiscan, Glucon, Glucolight, among others, battling for position – we expect to see real movement in this area in 2007.

- **NicOx—New insulin sensitizer in development**: NixOx announced July 26 that it intends to move its insulin sensitizing agent NCX 4016 into more extensive phase 2 studies. NCX 4016 combines the insulin-sensitizing effects of nitric oxide and salicylic acid in a sustained-release formulation. In a phase 2a trial presented in late 2005, NCX 4016 was shown to improve insulin sensitivity as measured by a hyperinsulinemic euglycemic clamp study in 13 patients. There's a huge market for any insulin sensitizer that displays fewer side effects than TZDs or metformin; NCX 4016 targets a different pathway than either so it could potentially fit the bill.
- **Nektar 2Q06— Betting on Exubera:** Nektar's quarterly earnings report on August 3 reported total revenues of $60 million ($44.2 million in product sales and royalty) fueled by Exubera product stocking sales to Pfizer. Nektar announced the closing of its Bradford UK site on July 26, and it's placing its hopes on Exubera. CEO Robert Chess defined the company's current goals as development of proprietary products, Exubera results, and forging high-value partnerships. Though Exubera seems ready to gear up (see Pfizer, "regional rollout"), it'll take some time before the market size becomes clear – reimbursement plans will be most important to obtain and interpret. For now, we think every day that Byetta is being sold and Exubera is not is a negative for the Pfizer/Nektar partnership since each new patient to use the pen means one less potential patient to market to using the anti-injection marketing. Yet and still, we do believe if safety were proven and if many more people with A1cs higher than average (>9.3) went on Exubera (Byetta wouldn't most likely be able to get most people with A1cs at that level to goal), the population A1c would decline, perhaps dramatically. And at the end of the day, that's the main goal. For that to occur, however, reimbursement needs to be in place, and we're skeptical on that happening anytime soon.
- **Mannkind—Seeking to stand out among inhaled insulins:** At the quarterly earnings report on August 3, Mannkind reported that its Technosphere Insulin (TI) System for inhaled insulin delivery, currently in phase 3, is on track for 2008 filing and launch in 2009.Lilly and Alkermes' inhaled insulin program is probably on a similar schedule, so it'll be catch up for market share with Exubera already out. Mannkind is looking to position TI as superior to Exubera, not just a "me too" drug by touting better pK, fewer postprandial excursions, and importantly, no weight gain – it will be very interesting to see if that persists in future trials. It would be a key benefit, although better still would be an insulin that makes people *lose* weight – that's the ticket! We learned on the call that Mannkind conducted a survey of 425 doctors to test the waters for TI. Of the 125 diabetologists, 150 internists, and 150 GPs, MKND felt all were supportive of TI's key attributes (inhaler, powder formulation, rapid pK, 2x fewer post prandial excursions). We're not totally convinced that it will be that different from Exubera – but Mannkind reported a survey of 425 doctors in which 41% of diabetologists, 40% of internists, and 48% of GPs expressed willingness to use TI . Furthermore, 10%, 7%, and 10% respectively were willing to use TI *ahead* of diet and exercise as a means to achieve better glucose control. At the least TI is different enough that management expressed no concerns about Novo's IP suit against Pfizer. Novo even conceded that its issue might be specific to Exubera.
- **Biodel—Hoping to overtake analog market with super-fast VIAject**: Biodel announced $21 million in Series B financing on August 2 – the company will be funded by lead investor Great Point Partners, a new healthcare investment firm managing both private and public equity funds; private equity powerhouse Orbimed; and Vivo Ventures. The company is developing a rapid-acting injectable insulin called VIAject which is currently in phase 2 trials. VIAject is a new formulation of regular human insulin, which more strongly favors the monomeric form and which, if it works, will be positioned as a more physiological form of preprandial insulin. Phase 1 results presented at ADA showed maximum absorption for VIAject at 30 minutes after injection compared to 60 minutes for Humalog. This was verified in double-blinded phase 2 results, albeit with a small number (n=14) of type 1 patients – phase 3 trials begin shortly. We think that this could be a very successful product for controlling postprandial glucose more closely – especially important with recent discussion of glycemic variability. Biodel appears interested in tapping into the vast market of type 2 patients who should be on insulin but are not – there is also an oral insulin called Viatab in pre-clinical laboratory models, intended for sublingual delivery. This could be especially worth watching – it has the noninvasive charm of inhaled insulin without the difficulty of complex delivery technology.
- **Novo Nordisk 2Q06—Diabetes care on a roll:** Novo's diabetes care business generated $1.2 billion in revenue this quarter, as reported at the quarterly earnings call on August 2. Revenue rose 17% from last year and represents 68% of overall growth. Novo's market share is a whopping 38% of the insulin

analog market – not bad since Novolog has only been launched since c. 2000 (versus Humalog in 1996) and Levemir launched only in March. Novo's new long-acting analog is said to be catching 5% of new Rx and 3% of total Rx basal insulin prescriptions. Aggressive marketing should continue to increase this. In the pipeline, Phase 2 trials for liraglutide (Novo's GLP-1 in development) are said to be going well – a trial in Japan with 200 non-obese type 2's showed an average A1c drop from 8.3% to 6.4% when switched from diet or OED therapy to liraglutide. The drug showed weight neutrality, no hypoglycemic events, no dose dependency, and few GI issues. Phase 3is planned for the first half of 2007 in Japan – the 'no weight loss' would be a big competitive disadvantage, so we continue to watch this front. Of note, NovoRapid (that's Novolog in Europe) was approved for pregnancy in the EU in July – significant, considering the dearth of pregnancy studies and *no one* wants to do them. Although there was news that Novo filed a lawsuit against Pfizer regarding inhaled insulin IP, there wasn't really anything explicit on what the suit was – really just that Novo's acquisition of Aradigm was the source of the intellectual property at stake in the suit. Interestingly, outside the US, Russia and Turkey were mentioned as drivers for insulin analog growth. China and Egypt were mentioned as drivers for human insulin growth; of note, Novo mentioned an improving reimbursement landscape in China.

- **Alizyme—On to phase 3 for cetilistat!** UK-based Alizyme announced on August 2 the successful completion of its phase 2 trials of cetilistat with the FDA. Cetilistat is a gastrointestinal lipase inhibitor, which works in the gut through an inhibition of enzymes involved in fat digestion in order to prevent the absorption of calories as fat. Cetilistat acts peripherally, unlike the majority of its predecessors. Obesity drugs that affect the central nervous system have been shown to cause side-effects associated with the brain, such as nausea and dizziness. As a peripherally-acting drug, cetilistat appears to offer a good safety profile over a wide range of doses. The FDA has approved Alizyme's plans for cetilistat's phase 3 program, which will dose approximately 4,000 patients for one year. The primary endpoint for the drug's obesity trials will be patients who lose at least 5% of their body weight. Other key endpoints include absolute weight loss and a reduction in co-morbidity with type 2 diabetes.
- **VeraLight—Sixty-second diabetes detection on the horizon?** VeraLight announced on August 1 the completion of its Series B financing by Psilos and CMEA and other previous investors. The company raised $17.5 million for its VeraLight Scout diabetes screening system, which uses noninvasive fluorescence spectroscopic technology to screen for pre-diabetes and type-2 diabetes. The 10-lb device scans patients' forearms and requires just 60 seconds to give a result, so it looks like they will position it as a more accurate and convenient method for screening diabetes than the fasting glucose test. An initial trial presented at ADA compared the device to a standard fasting glucose test in 328 patients at risk for diabetes or pre-diabetes. Results showed that the Scout identified 20% more pre-diabetes and type-2 diabetes patients than the fasting glucose test. We think this technology could do a lot for identifying type 2 patients, especially early in the disease when beta cell function can be more easily preserved. One of our recurring themes is the importance of convenience both for patients and PCPs, so if this device is perceived as more convenient than conventional tests, PCPs will be more likely to us it.
- **Sanofi-Aventis 2Q06—Acomplia launch in US planned for 2006 and FDA interaction "very intense and regular":** In its August 1 earnings report, Sanofi discussed many products of interest, most notably Acomplia and Lantus. Acomplia launched in the UK on June 29 - no direct sales figures yet but we do know it's set to launch in Germany in several weeks. Sanofi's survey from April/May found that 77% of physicians in the US, compared with 89% in the UK and 84% in Germany, said they would prescribe Acomplia for cardiovascular problems, while 19% of US physicians said they would prescribe it for weight loss only. It seems 45% of physicians in the US, 41% in the UK, and 64% in Germany said that intra abdominal obesity is "credible" as a risk factor for CVD, with more than 90% aware of the concept. We think there's big potential if Sanofi convinces more physicians that obesity alone is an indication. As for the launch, as a reminder Acomplia on Feb 17 received the non-approvable letter for the smoking indication and the approvable letter for weight management. Little information has been given about resubmission, but management expressed hope for launch by end of the year – that would be something! But there's not much evidence that will happen. In other news for Sanofi, the company reported at the quarterly earnings call on August 1 that US pharma growth was 3% for the first half, or 23% excluding the impact of the loss of patents on four products. One of these was Amaryl, which had a sales drop of 38.7% from Q205 (the oral type 2 drug is now generic). However, Lantus sales were up nearly 50% in the US and commands more than 30% of the US insulin

market. This puts it in the lead in the overall US insulin market. Novo said it had "no information at all on an advisory committee." Hans Peter Spek, who heads up pharmaceutical operations, said that his understanding is that an advisory committee could always appear, but that today he has "not the slightest indication" that the FDA plans to hold one. Meanwhile, like with DPP-4s, we can't imagine no panel meeting *except* that (see Merck, below) since the panel meeting process is broken, perhaps they will just be skipped in diabetes this year. Sanofi is in ongoing discussions with the FDA, it said. Spek said there is a continuous dialogue in which Sanofi submits information and the FDA may ask additional questions on what has been submitted. He said, cryptically, that the process is going on in a "very intense and regular manner." (We think intense is the same as regular, but by and large, we don't think most people do.) Lantus has the lead in the overall US insulin market. In the second quarter, Lantus's revenues were 421 million euros, an increase of 40% over Q205 (all changes calculated "on a comparable basis," or correcting for fluctuations in exchange rate). Compared to the year-ago quarter, Lantus sales in the US were up nearly 50%; Europe's sales increased by 20%, and sales in the other combined countries rose by 70%. Lantus' sales totals for the first half reached 803 million, an increase on a comparable basis of 41%. The press release highlighted two studies presented at ADA: the APOLLO study pitted Lantus and oral agents against short-acting insulin lispro and oral agents and found that Lantus was "as effective with less hypoglycemia" as lispro. A second study found that an algorithm to calculate mealtime insulin based on pre-meal glucose values alone, and as an alternative to carbohydrate counting, was just as effective as carb counting.

- **Merck—Not once but twice! Beating expectations on DPP-4 Januvia/Metformin**: Merck announced on July 31 that the FDA had accepted its MK431A filing for sitagliptin plus metformin in combo therapy. The targeted file date for this was moved from 2007 to 2006 at ADA, but Merck has beat expectations by getting it so early in the second half of the year. MK431 for sitagliptin was itself submitted in mid-December, and an answer is expected in mid-October. It will be interesting to see if the combo therapy is more limiting than monotherapy because Metformin does have GI side effects in ~30% of patients. We think Merck will probably go for first-line therapy on this. It has been positioning Januvia as "enabling the body's own system to do the job it is designed to do" and the 431A combination as "there's a big need for combo therapy and this is a great alternative." Combo therapy, of course, has been a big theme of late, and from a patient perspective, the one pill per day / one co-pay will make the combo seem more favorable, which will aid compliance, making clinicians happy. Merck said it won't have data on this at EASD, as the filing deadline was too early (April 1).
- **Merck 2Q06 – Panel or no panel?**: In comparison to the MK431A news, Merck's quarterly earnings report on July 24 was rather less interesting. Management mostly reiterated sound bites from ADA and still pointed to mid-October for FDA action on Januvia. As for a panel meeting, Merck doesn't have new information there either. We personally can't imagine there won't be one, and the question is, will FDA do a Novartis/Merck meeting at the same time? On the positive side for Merck, there does seem to be growing acknowledgement that the panel advisory process is broken (we would agree) and so perhaps since it isn't "fixed" yet there's more likelihood it would be skipped. One analyst asked about submissions in Europe, and Merck declined to answer.
- **Becton Dickinson 2Q06—Marching toward triple digit blood glucose revenue goal**: At the quarterly earnings report on July 28, BD highlighted double digit sales in the US in diabetes care (they weren't more specific, but this is higher than some competitors albeit from a much lower base than most counterparts). BD Medical grew 6-7%; BD diagnostics grew 6-8%, and the company said it was still investing strongly in pen needle lines. BD continues to benefit enormously from Amylin's new products as it makes the pen needles; the anticipated impact of Amylin's self-imposed Byetta slowdown never materialized because Amylin beat all expectations handily for Byetta (so pen needle sales didn't slow). Management reported that BD Diabetes revenues were driven by the pen needles business – we say largely by Byetta. The revenue in blood glucose monitoring – we always listen for this number for our model – was $29 million. Management said it was not expecting dramatic change going forward, but they do still expect to be around their guidance number of $115 million for the year. Given all that has changed in blood glucose monitoring (mail order, competitive bidding, managed care pricing pressure, etc.), we might expect BD to exit the blood glucose monitoring business if industry forces don't improve.
- **NeuroMetrix 2Q06— A small slice of the diabetic neuropathy market:** NeuroMetrix's medical device, the NC-Stat System, diagnoses neuropathy through nerve conduction studies. For the moment

only about 25% of customers are using it for diabetic peripheral neuropathy (DPN); the system can be used to detect a number of other neural problems unrelated to diabetes. The company reported on July 27 that quarterly revenues were up 73% from last year figure of $14 million; the customer base was up 50% to 4,068 active customers. If NeuroMetrix can position this product as the primary tool for DPN, it could do very well in sales (consider the number of diabetes patients at risk for neuropathy), but that's a very big if.

- **AstraZeneca 2Q06— More combo therapy: anticipating Crestor/Tricor, albeit in 2009:** Oddly, no mention was made of the pipeline at the quarterly earnings call on July 27, but several items from AstraZeneca's press release are worth noting: the preclinical compound AZD1092 and the phase 3 Galida (their dual-acting oral peroxisome PPAR agonist for metabolic syndrome / diabetes) have both been discontinued. We think the latter is a big disappointment – dual PPAR agonists, if successful, would have been a huge alternative to TZDs. In the pipeline is a possible line extension for its angiotensin II antagonist Atacand, which is under phase 3 investigation for diabetic retinopathy. This is planned for NDA filing after 2008, as are three other drugs in phase 1: AZD2479, a reverse cholesterol transport enhancer for dyslipidaemia, AZD6610, PPAR alpha with "partial gamma" modulator for combined dyslipidaemia, and AZD8677, for dyslipidaemia and diabetes. AstraZeneca won't have anything in diabetes expected to file before 2008 so it's looking like a pretty sparse diabetes pipeline from them for the next few years.
- **Polymedica 2Q06—Solid customer base for steady sales:** With an emphasis on providing mail-order, direct-to-consumer blood glucose testing supplies and related products and services to seniors who have diabetes, Polymedica can only benefit from the growing size of its target patient/customer demographic. Not surprisingly, quarterly earnings reported on July 26 were up 52% to $156 million; the company added 54,000 new patients thanks to its TV marketing campaigns and to the acquisition of three diabetes companies serving about 23,000 patients. Now what would really drive up earnings for this company is if seniors with diabetes tested more often. At any rate, we foresee continuing growth for the company on the basis of customer growth alone.
- **GlaxoSmithKline 2Q06—Avandia on fire, moving into first line therapy:** A 10% rise in GSK quarterly earnings, reported on July 26, was driven by strong sales in the US; sales for the Avandia franchise increased by 32%, up to 477 million pounds ($882 million) - huge result! - with a relaunch of Avandamet in Q2 after resolution of supply issues. This June also saw European approval of Avaglim (GSK's new combination of Avandia and Amaryl). We've been talking a lot about how monotherapy is basically dead - GSK and Takeda both benefit from the combo trend. We think this is especially welcome to PCPs, who seem to love anything easier. GSK is in phase 3 trials for Avandia XR (rosiglitazone XR) as a treatment for Alzheimer's disease. Also in phase 3 is Redona (denagliptin), GSK's new DPP-4 inhibitor. Investors were interested in seeing phase 2 data on the drug, but management deferred on release of the results. We figure the data won't be that impressive, but we think it's a big market and easy to use so barring safety problems, they could do well – reimbursement, however, is the other big concern. Earlier in the month GSK also announced a new FDA first-line indication for its Avandia/metformin combination single-pill drug, Avandamet. This indication could increase sales for the Avandia franchise since there are currently no other combination pills with first-line therapy indications, although a similar combination pill, Takeda's Actosplus Met, has a second-line treatment indication. Dr. Barry Goldstein (Jefferson University), a leading endo and a consultant to GSK, has advocated using Avandamet primarily in diabetes patients early in treatment to avoid side effects and disease progression. Certainly, there is a possibility that TZD therapy, and hence Avandamet, will be used in pre-diabetes to prevent or slow disease progression. But we don't think the FDA will move fast on this, and we don't think TZDs will be used much off label for this by PCPs. But DREAM and ADOPT are highly-awaited clinical trials in which TZD use is analyzed for its ability to halt progression to diabetes from pre-diabetes and as a first-line therapy in newly diagnosed type 2 patients. Look for DREAM results at EASD in September in Copenhagen and ADOPT in Cape Town in December.
- **Arena 2Q06—Fast phase 3 initiation planned for Lorcaserin:** Arena devoted the majority of its quarterly earnings call on July 25 to detailed discussions of its oral obesity drug lorcaserin (previously APD356), the company's most advanced product in development. CEO Jack Leif reported phase 2b study results showing that the drug causes no QT interval prolongation, an adverse cardiac effect, even at 2.5x the maximal therapeutic dose. Lorcaserin showed progressive, dose-dependent weight loss and

reductions in BMI and waist and hip circumference at 12 weeks. Interestingly, positive changes in fasting glucose and lipid measures were observed despite normal mean baseline values. So, one of the three pivotal trials planned for phase 3 studies will be conducted in type 2 patients. The first pivotal trial, to be 2 years in duration, will enroll a whopping 3,000 patients without diabetes starting September/October of this year. Enrollment is expected to be complete within a quarter, and Arena will decide based on the trial's six-month performance measures whether to proceed with the other two pivotal trials in 2007. Arena is moving very aggressively on this trial program; it estimates $125 million in external expenses over the 2.5 years the program will require (about $30 million of it in 2H06). Considering the dearth of obesity drugs currently on the market, Arena is positioned to do very well if lorcaserin makes it to the expected 2009 NDA file date and receives reimbursement. The main question for now is whether these phase 3 studies will reveal any safety problems. We'll be watching for the six-month benchmark in 1H07. Arena is also developing APD668 for the treatment of type 2 diabetes in collaboration with Ortho-McNeil, a Johnson & Johnson company. APD668 is in phase 1 trials; it targets the glucose-dependent insulinotropic receptor (GDIR), a novel receptor that stimulates insulin secretion in a glucose-dependant manner. It's too early to say much about this drug's potential, but in the world of polypharmacy any compound that has a novel target route can gain considerable market share. We'll see if this drug makes it into more advanced trials.

- **Amylin 2Q06—Byetta sales at ~$100 million, Symlin sales exceed $10 million:** Quarterly earnings reported on July 24 exceeded analyst forecasts with Amylin's total revenue at $118.1 million for the quarter ending July 30. Of that, $98.6 million came from Byetta sales and $10.2 million from Symlin. Demand continues to grow - over 1 million (a million!) prescriptions for Byetta have been filled as of the end of June, and over 50,000 physicians have prescribed Byetta since its launch. On the supply side, both suppliers, Wockhardt and Baxter, will be increasing their production. As Amylin is able to expand supply, it will reinitiate vouchers, tell HCPs they can begin new patients on Byetta, and begin to produce samples. In anticipation, the field force will expand by 130 to 550 by the end of this year. The company is developing a possible new indication for Symlin in combo with basal insulin expected in early 2007. A Symlin pen is also being submitted for application; this is also anticipated for 2007 – users will cheer. A study of Byetta in monotherapy is underway – if all goes well Amylin is expected to submit to the FDA in early 2008 with an anticipated six-month review. Room temperature storage instructions for Byetta are being negotiated with the FDA for early 2007. The exenatide LAR trial is on track with enrollment; Amylin will likely begin manufacturing by late 2008. Amylin is testing exenatide for nasal delivery in partnership with Nastech – this is still in phase 1. A study of pramlinitide and leptin for obesity is in phase 2 – we'll wait on results for that in Q4.
- **Schering-Plough—Strong cholesterol franchise; taking aim at Crestor with Vytorin:** The quarterly earnings call on July 24 featured much discussion of the company's cholesterol franchise, going strong with global growth of $90 million in revenue, up 85% versus a year ago. Zetia's growth is going strong with still-increasing prescription demand, but Vytorin alone represents more than half of Schering-Plough's United States cholesterol franchise sales, and the entire Schering-Plough cholesterol franchise ranks second for total prescriptions with a share of 15% despite patients switching from brand name statins to sympostatin, the new generic on the market. Pharma head Carrie Cox presented some interesting data showing that Vytorin provides greater LDL reduction than Crestor, especially in high-risk populations. With generics cutting into market share, it sounds like Schering is planning to fight Astra-Zeneca for brand-name prescriptions.
- **Eli Lilly—Byetta boosts franchise revenue growth considerably:** Management reported on July 21 that overall quarterly diabetes franchise revenues were $702 million, up 5% over last year's $669 million. Lilly guided to the low end of revenue for Q3 and year-end, with very ambitious expectations for the insulin franchise as one of the causes. We had been confused last year when they talked about re-energizing their insulin franchise (how?!), and so we didn't find this very surprising – Novo results (Novolog) and Sanofi results (Lantus) confirm the very tough competitive landscape. Humulin sales fell – competitive pressure and lack of demand – though Humalog sales were up, surprisingly. Actos sales were also down. We calculate that without Byetta, sales would have dropped 3% rather than increasing 5%. Still no word on the needle gauge for exenatide LAR. Lilly signed a deal with Alcon to co-promote Arxxant, its new drug for diabetic retinopathy. Approval expected "next month".
- **DexCom 2Q06—Steady, on:** CFO Steve Kemper reported disappointing revenue at the quarterly earnings call on July 20: $479,000 for 2Q06, or a net loss of $11.2 million for the quarter. This may

reflect low "repeat" orders and fewer sales than expected of primary gear. We don't view this as surprising, since the absence of reimbursement is a major barrier, as has been discussed. DexCom presented with Medtronic and JDRF at an April CMS meeting, and two letters signed by members of Congress were recently sent to the HHS secretary, stressing the need for this technology. The STS study conducted by Garg et al was cited in the letter. Personally, we don't think that study alone will warrant change but directionally, it is certainly promising. There will be an MCAC (Medicare Coverage Advisory Committee) meeting on August 31 to evaluate glucose monitoring in general, and DexCom is submitting written materials for that meeting, potentially presenting on data. A few payers (Blue Cross Blue Shield, United, Prudential, and Aetna) have reimbursed individual patients, but these are isolated cases and we believe full reimbursement is still a good ways off. In the mean time, DexCom has begun targeting regional diabetes centers with its 25-person sales force and a good 80% of sales in June came from just 45 regional centers, with demand outstripping supply temporarily near the end of June. CEO Andy Rasdal said the issue of three-day sensor cut-off capabilities might need to go before the FDA. Impressively, the PMA supplement for the 7-day STS was submitted during the second quarter, and the 7-day device will have improvements in addition to the longer duration: better accuracy and stability, smaller needle size, a waterproof claim, next generation algorithms, BG meter brand neutrality, and more robust end-of-use shut off. We believe the latter two changes will be very important. Further off: pediatric and long-term sensor feasibility studies are underway – we'll be interested in hearing results of these trials in the future. All in all, very good news over the longer term for the company.

- **Pfizer—Pfizer announces another (final?) delay in Exubera launch:** Originally inhaled insulin was to launch mid-June, then mid-July, and now there may be another delay, reported by management at the quarterly earnings on July 20. Some pharmacies expect it in August, We are interested to hear the reactions of early adopters -- reimbursement is a necessary but not sufficient condition for successful launch, and early success. Safety remains a big question in addition to reimbursement - it seems PFE isn't close to success at this point.
- **Roche/Ipsen—Roche gets serious with GLP-1; diabetes franchise lags:** Roche in-licensed a GLP-1 compound from Ipsen on July 21 that is currently in phase 2 studies. Ipsen will receive ~60 million Euros now and up to 170 million Euros with milestones and progressive milestone payments. This compound is said to use a 29-gauge needle (we were surprised they could tell that this early although we doubt it is finalized) and to have dosing once every two weeks, not once monthly as earlier said. This still compares favorably to Amylin's LAR, which will have once weekly dosing, but not as favorably as once monthly would have been. We think timing will be everything. *** At Roche's quarterly earnings call on July 20 CEO Severin Schwan of the Diabetes Care division explained weak first half earnings by saying that Roche had rolled out the next generation of its Accu-Chek platform – Aviva and Compact Plus – during the first quarter. Sales in the North American region for 1H06 were only $323 million, down 9% from 1H05 sales. We can only imagine how bleak Q1 must have been to achieve a 9% decline for the half year given meaningful acceleration in Q2 as the new Accu-Chek products started stimulating sales of higher-margin strips. Of course, the new monitors, especially the integrated Compact Plus, are more expensive to make as well. Accu-Chek historically does less well in the second half because more monitors are placed in Q4, and these have a lower profit margins than strips, as mentioned above.
- **Abbott—Diabetes franchise revenue up 10%** with growth in diabetes care up 9.6% overall, reported at the quarterly earnings call on July 19. Management said it believed that its glucose monitoring business is about to assume the #2 position in the US and #3 position worldwide behind LifeScan and LifeScan and Roche, respectively. Wow, that would be something! The launch of Freestyle Freedom, a follow on to the FreeStyle, should build more momentum going into the second half of the year though there are also other new meters (LifeScan's Ultra2) coming out as strong competition. The small sample size (0.3 ml) and easy-to-read display are meaningful advantages for patients – and the core of Abbott's marketing message. Management noted it expected FDA approval for Navigator in late Q3 or Q4 but implied it did not expect sizable early revenues. Absent reimbursement, we don't expect heavy buying either (see DexCom, above). However, Abbott has secured four major managed-care accounts, which would take effect in Q3. In drug news, in the works is a collaboration with Astra-Zeneca to make a new combination pill, a fixed dose combination statin/fibrate (Crestor/Tricor or Abbott's follow on fibrate ABT-335 - the combo is TBD). This reinforces the growing importance of polypharmacy

and ease of use. This drug will be positioned as use for total cholesterol management (LDL, HDL, TriG) and is slated for 2009 release.

- **J&J—Tough to defend the top position, but Animas provides boost:** This quarter continued the trend that LifeScan's growth is weaker than that of competitors, namely Bayer and Abbott, though Animas's growth was strong – terrific, given Medtronic and Insulet competition. J&J credited Ultra at the earnings call on July 18 for its international sales growth. We believe they also benefited from Ultra2 stocking. Any growth in blood glucose monitoring right now is positive given the challenges the industry is facing – namely pricing pressure from managed care, more competitive pressure, the concerns about competitive bidding, coming competition from continuous with the most profitable users, Byetta customers, testing less, etc. J&J has three compounds in-licensed with Metabolex – this will be very interesting to watch. Management emphasized the dual PPAR metaglidasen; it is an insulin sensitizer in phase 2/3 trials. Phase 2 results showed good tolerability; it lowered blood glucose, triglycerides and uric acid levels without weight gain or edema – it will probably be billed as a better, safer TZD. It sounds like Metabasis has just one more year of toxicology studies to complete, but launch probably will not occur before 2010 because of the extensive phase 3 trials that will likely be required. DREAM trial results on September 15 at EASD should show whether rosiglitazone (Avandia) and/or ramipril prevent the onset of type 2 diabetes, which would have implications for metaglidasen.
- **Medtronic—More magic timing - FDA approval for Guardian next-gen RT:** Medtronic received FDA approval for Guardian RT as stand-alone sensor on July 17. The 522/722 pump has been shipping since April, and the sensor/transmitter that is part of that system has been shipping since June 19. Unlike the pump alone, this product has predictive alarms and rate of change alarms. Medtronic says that CGM technology is far more sensitive to glucose excursions than traditional blood glucose monitoring – we agree. Other features that are attractive to users are that it is waterproof and has expanded trend analysis capabilities. The Medtronic CareLink software will probably play a large role in the marketing of this device, as it has received strong feedback, especially relatively speaking. Medtronic plans to launch by the end of the year, so it won't immediately compete with DexCom. There is no pricing information yet. Medtronic will show this product at AADE, so we will look forward to checking it out in LA this week.
- **Novartis—Galvus … more data than Januvia?** Management at the quarterly earnings call positioned Galvus as one of the leading compounds in the Novartis pipeline. Galvus is expected to receive FDA approval in December and to be ready for launch in 2007. (Merck expects an action date in mid-October for its competitor DPP-4 inhibitor Januvia.) Novartis is emphasizing Galvus's superior efficacy, body weight profile, and tolerability compared to TZDs. The drug does well in combo with metformin, which is likely how it will mostly be used – the ADA mantra: monotherapy is dead! Novartis' trial results still suggest relative weight neutrality (compared to Byetta) with possibly a small weight loss in heavier patients. We'll be waiting on the GLORIOUS mega-trial results for the question of whether DPP-4's really protect beta cells.
- **Northfield Laboratories—PolyHeme for islet transplants**: Dr. Jose Avila of the University of Illinois at Chicago presented a paper at the World Transplantation Congress on July 27 reporting the successful use of Northfield's PolyHeme human hemoglobin-based oxygen carrier in pancreatic islet cell isolation and transplantation. The preclinical study, conducted in small animals, was led by Dr. Jose Oberholzer, Director of Cell and Pancreas Transplantation at the University of Illinois at Chicago and Director of the Chicago Project. It showed that use of Northfield's PolyHeme improved islet cell function and transplantation outcomes. If future studies show the technology prolongs islet function after transplantation, it may become very useful in future islet transplants.

—Kelly Close, Aviva Gilbert, Cindy Glass, Jenny Jin, Erin Kane, Nupur Lala, Patty Pringle, and Win Rosbach

8. DCU's Literature Review Column

We are excited to introduce a new feature in Diabetes Close Up: the Literature Review Column. Starting with this issue, we will provide a list of the top diabetes-related articles for the month, as well as at least

one in-depth review of a key article. We are constantly scouring the major medical journals for key diabetes-related articles, and we hope you find this list of use. Below is our list of the top 10 articles from June and the top 15 articles from July on diabetes, from journals such as *Diabetes Care, NEJM, JAMA, The Lancet, Pediatric Diabetes*, and more.

June 2006

- *Diabetes*- Chronic Inhibition of DPP-4 With a Sitagliptin Analog Preserves Pancreatic β-Cell Mass and Function in a Rodent Model of Type 2 Diabetes - Mu et al
- *Diabetes Care*- Comparison of the Glycemic Effects of Rosiglitazone and Pioglitazone in Triple Oral Therapy in Type 2 Diabetes - Tran, Navar, Davidson
- *Diabetes Care*- Health Care and Patient-Reported Outcomes: Results of the cross-national Diabetes Attitudes, Wishes and Needs (DAWN) study - Rubin
- *NEJM*- Food Marketing and Childhood Obesity – A Matter of Policy - Nestle
- *NEJM*- Obesity – The New Frontier of Public Health Law - Mello
- *Pediatric Diabetes*- Insulin pumps in pediatrics: We have the technology. We have the evidence. Why are still so few kids using it?- Danne, Tamborlane
- *Pediatric Diabetes*- Fulfilling the promise of insulin pump therapy in childhood diabetes - Tamborlane
- *Pediatric Diabetes* - The selection of children and adolescents for treatment with continuous subcutaneous insulin infusion (CSII) - Fisher
- *Pediatric Diabetes* - Emerging evidence for the use of insulin pump therapy in infants, toddlers, and preschool-aged children with type 1 diabetes - Weinzimer
- *Pediatric Diabetes*- Cost-effectiveness of continuous subcutaneous insulin infusion (CSII) in children: illusion or delusion - Nuboer, Bruining

July 2006

- *Ann Int Med*- The Association between Quality of Care and the Intensity of Diabetes Disease Management Programs - Mangione et al
- *Clinical Chemistry*- Inflammation and Changes in Metabolic Syndrome Abnormalities in US Adolescents: Findings from the 1988-1994 and 1999-2000 NHANES - Ferranti et al
- *Clinical Diabetes*- Exuberance Over Exubera - Hite, Barnes, Johnston
- *Clinical Diabetes*- Hypoglycemia in Type 1 and Type 2 Diabetes: Physiology, Pathophysiology, and Management - Briscoe, Davis
- *Clinical Diabetes*- Evaluating The Therapeutic Package for Diabetic Patients: The Whole Exceeds the Sum of Its Parts - Leichter
- *Diabetes Care*- Continuous Glucose Monitoring–Guided Insulin Adjustment in Children and Adolescents on Near-Physiological Insulin Regimens - Yates et al
- *Diabetes Care*- The Effect of Glucose Variability on the Risk of Microvascular Complications in Type 1 Diabetes - Kilpatrick, Rigby, Atkin
- *Diabetes Care*- Glucose Variability and Complications - Bolli
- *Diabetes Care*- Risk Associated With the Metabolic Syndrome Versus the Sum of Its Individual Components - Sundstrom et al
- *Diabetes Educator*- Psychological Insulin Resistance: Overcoming Barriers to Starting Insulin Therapy – Davis, Renda
- *Diabetes Tech & Thera*- Incretin Mimetics and Dipeptidyl Peptidase-IV Inhibitors: A Review of Emerging Therapies for Type 2 Diabetes - Kendall, Kim, Maggs
- *Diabetologia*- Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy - Nathan et al
- *The Lancet*- Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people - Booth et al
- *NEJM*- Lack of insurance hinders Americans' diabetes care - Boddiger
- *JAMA*- Effect of Youth-Onset Type 2 Diabetes Mellitus on Incidence of End-Stage Renal Disease and Mortality in Young and Middle-Aged Pima Indians - Pavkov et al

You may recall that one of our top takeaways from ADA was the need for more aggressive therapy. The article we highlight in this month's literature review echoes the sentiments of the many speakers at ADA who pushed for much earlier, more aggressive approaches to get diabetic patients to lose weight and to get

under control. In July, ADA and EASD jointly published a new consensus statement on hyperglycemia management in type 2 diabetes in *Diabetologia* and *Diabetes Care.* This statement offers a straightforward algorithm for getting type 2 patients under control as quickly as possible. We think the algorithm could be better (it doesn't include Byetta or Symlin, which many patients would want), but the emphases on combination therapy and early initiation of insulin are welcome ones that we hope health care providers will heed.

Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, Zinman B. "Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy." Diabetologia Aug 2006. 49:1711-1721* and *Diabetes Care Aug 2006. 29:1963-1972.

This consensus statement by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) sets new guidelines for the glycemic goals of type 2 diabetes management:

1. achieving and maintaining normal glycemic levels
2. initiating therapy with lifestyle intervention and metformin
3. rapid addition of more medications when over glycemic target
4. early initiation of insulin therapy when necessary

Notably, this consensus statement focuses primarily on HbA1c as the most useful indicator of successful treatment. An HbA1c > 7% should "serve as a call to action to initiate or change therapy." The authors note that, ideally, treatment targets should be in the non-diabetic range of HbA1c > 6.1%, but the focus of this consensus algorithm is simply to get HbA1c < 7%.

This article discusses all the medications currently available for type 2 treatment. However, the consensus algorithm does not recommend pramlintide, exenatide, α-glucosidase inhibitors, or glinides except for "selected patients" because of the higher cost, smaller glucose-lowering effects, and/or less extensive clinical data associated with these drugs. Rather, the consensus algorithm recommends the following treatments: lifestyle interventions, metformin, sulfonylureas, TZDs, and insulin, to be titrated in a stepwise manner as the disease progresses.

The consensus algorithm is diagrammed in detail in a flow-chart figure in this paper. It makes the following recommendations:

1. **Lifestyle interventions and metformin at diagnosis.** The authors recommend training with a dietitian to encourage patients to adopt lifestyle interventions such as weight loss and exercise. However, metformin should also be prescribed at diagnosis because most patients fail to achieve glycemic goals with lifestyle interventions alone. Nevertheless, lifestyle recommendations should continue to be a part of treatment recommendations at every stage because of their low cost and great efficacy.
2. **Additional medication every 2-3 months until HbA1c is < 7%. Then check HbA1c every 6 months.** For patients who still have HbA1c > 8.5%, the authors suggest insulin therapy as the next step because it is the most effective. For patients still over target with lower HbA1c, sulfonylureas are the least expensive treatment while TZDs have the advantage of not causing hypoglycemia.
3. **Further adjustments as necessary.** The authors emphasize the progressive nature of this disease, which will require increasing medication and insulin to control over time. If HbA1c is between 7-8% after adding a second medication, a third oral agent can be considered. However, adding or intensifying insulin is both more effective and less costly than triple oral therapy. The last and most advanced treatment in the consensus algorithm combines intensive insulin with metformin and possibly a TZD.

A flow-chart diagram for the initiation and adjustment of insulin therapy is also provided. Therapy should begin with 10 units or 0.2 units per kg of an intermediate- or long-acting insulin. Dosage is titrated upward by 2 units every 3 days (or 4 units every 3 days if fasting glucose > 10 mmol/l) until fasting levels are 3.89-7.22 mmol/l. If HbA1c is still not > 7% after 2-3 months, then pre-meal rapid-acting insulin injections should be added as necessary. The authors emphasize the importance of involving the patient as the primary caregiver in any insulin regimen, including the importance of self-monitoring of blood glucose (SMBG).

Other considerations in therapy are discussed. One consideration is that multiple therapies work best when they have different mechanisms of action. Especially good combinations are insulin plus metformin or insulin plus a TZD. For severely uncontrolled patients with fasting glucose > 13.9 mmol/l or HbA1c > 10%, the authors recommend rapid initiation and titration of insulin therapy. They also remind readers that when counseling patients to lifestyle recommendations or medication regimens, it is important to be sensitive to ethnic and cultural differences in patient populations.

In our opinion, the recommendations set forth in this paper do well to emphasize faster and more intensive adjustments to therapy for type 2 patients. However, the notable absence of exenatide and pramlintide in these recommendations is unrealistic and somewhat antiquated at this stage. GLP-1 and amylin mimetics are certain to become an increasingly important part of type 2 diabetes treatment in the future. The weight loss associated with these therapies is hugely important to type 2 patients, and the fact that they have only modest HbA1c-lowering effects can be solved by pairing them with other therapies.

—Jenny J. Jin and Katelyn L. Gamson

9. dLlife Shows You Must Not Miss!

We've been watching as dLife, the diabetes show, which continues to air on CNBC. The show, now in its second season, has garnered more than 400,000 viewers. Unlike a lot of summer television, dLife's line-up is not bad. We profile below what we see as the top three episodes of the season:

- We wouldn't miss the episode airing Sunday, August 20, which features Dr. C. Ronald Kahn of the Joslin Diabetes Center speaking on the genetics of diabetes. We reported on Dr. Kahn's presentations at AACE and ADA, and in this episode we expect him to translate his genetics expertise into something the layperson can understand. We're particularly interested in learning more about this topic, as we expect that medicine will focus increasingly on genetics-based therapeutics. The same episode includes a segment on how India is responding to the diabetes epidemic, a topic that has implications for the diabetes market for drugs and devices. India has the world's largest population with diabetes, with 32 million diagnosed in 2000, and this number is continuing to grow—the projected figure for 2030 is 80 million.
- Dr. James Gavin, a perennial favorite with colleagues, patients, and conference-goers (he has quite the commanding presence, which we saw yet again at the Novartis symposium at ADA this year), will be on air August 27. The preview promises that Dr. Gavin will explore the real reasons behind the explosion of type 2 diabetes in America – looking forward to hearing this.
- Our third pick for summer dLife watching has already aired but it will be rerun Oct 8 because three of the most interesting endocrinologists in the country appeared on the July 21 episode. Dr. Howard Wolpert debated the (in)famous Dr. Richard Bernstein, the type-1-diabetic-turned-MD of *Dr. Bernstein's Diabetes Solution*. Dr. Irl Hirsch appears in the same episode, discussing "high tech advances in patient care," no doubt an update on continuous glucose monitoring and insulin pumps.

—Erin Kane

10. Upcoming Conference Preview

- **AADE, August 9-12, Los Angeles, CA www.aadenet.org - see earlier this letter**
- **EASD, September 14-17, Copenhagen, Denmark, www.easd.org** EASD promises a wide variety of topics in both basic science and clinical care, including genetic prediction of diabetes, transcriptional and regulatory factors in glucose maintenance, treatment of complications, and closing the loop on an artificial pancreas. One big ticket item will be the highly awaited DREAM trial results, September 15, presented by Dr. Hertzel Gerstain. The study's purpose was to determine if rampipril and/or rosiglitazone would prevent the onset of Type 2 diabetes.
- **IDF 19th World Diabetes Congress, December 3-7, Capetown, South Africa, www.idf2006.org** ADOPT, another long awaited trial, will be presented here. ADOPT compares rosiglitazone monotherapy with metformin or glyburide/glibenclamide in disease progression, beta cell function or risk markers for macrovascular complications in recently diagnosed Type 2 patients.

—by Rachael Hartman

Diabetes Close Up is a newsletter highlighting notable information and events in the diabetes industry. This newsletter is put forth as an unbiased commentary on the industry and is not meant to serve as a recommendation to buy or sell (or hold!) any stocks. Companies that are current clients of Close Concerns include Abbott, Amylin, Bayer, Johnson & Johnson, Medtronic, and Roche and a number of small, private companies. If you would like to subscribe to DCU, see www.closeconcerns.com. More information and disclosures found on our website www.closeconcerns.com.