DIABETES CLOSE UP

Diabetes Close Up
March, 2007, No. 67
The Diabetes Pandemic: Marching Toward a Billion

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

From the Editor:

Those of us in the diabetes community take for granted that leaders at home and abroad recognize the scope and seriousness of the disease. But that assumption is dangerous and very far from the truth. We were reminded of this when we attended Novo Nordisk's Global Changing Diabetes Leadership Forum in New York on March 13. *The keynote speaker, Bill Clinton, shared a fascinating – and in some ways, self-damning – story with us. He explained that a month before he was inaugurated as president, his first campaign manager – from an ill-fated Congressional race in 1974 – died of complications from diabetes. So Clinton took office knowing how devastating the disease can be, but he nonetheless didn't realize the extent of the epidemic. As president, he said, you see the headlines but miss the trend lines. Well, it now appears he has seen the trend lines, at least in diabetes, and he has pledged that the Clinton Foundation will work with Novo Nordisk and others in attacking the problem. Check out our story about the Forum, as well as our feature interview with Novo Nordisk CEO Lars Sorensen. Sorensen blew us away at the Forum as well as in a wide-ranging conversation that focused on Clinton's talk, global awareness of diabetes, healthcare investment, the company's new products in development, self-inflicted wounds by the pharmaceutical industry, insulin in developing countries and broader international efforts such as the UN Resolution on diabetes and diabetes prevention. Now that's leadership.*

Merck got approval for Janumet earlier this week! *There was some doubt about whether the FDA would grant approval considering the delays that it has placed on Galvus, so we held our March issue*[1] *'til we found out for sure. We think Janumet could potentially help patients who quickly fail monotherapy – a group that makes up a fairly large portion of initially diagnosed type 2 patients (see the Cook et al paper in our lit review column on page 30). On a related note, incretins are also making headway in Europe. This year's Diabetes UK was very much a "Byetta meeting," as excitement builds toward the UK launch on May 1 – some very proper British doctors were practically frothing at the mouth (to say nothing of nurses and patients)! On the DPP-4 inhibitor front, Merck got EU approval for Januvia on March 26 – yes, it's on a roll. After Januvia's very strong US execution throughout its autumn launch, we assume Merck will move quickly in Europe as well.*

The CMS competitive bidding ruling came out this week as well – we perceive it as good news for the major blood glucose manufacturers*. Please see our short story in "In the News" – we'll provide a more detailed look at this ruling in our next issue.*

Excitement abounds! The upcoming month is PACKED full of interesting conferences*! We'll be heading to AACE in Seattle come mid-month (April 11-15), where we expect to see new guidelines on postprandial glucose unveiled. This will be a **wow** moment, if it is, as we expect, a most welcome step away from the current A1c-centric thinking. Late this month we'll attend what we expect to be a*

[1] Our date says March/April, but there will be a full April issue later this month – just in case you were worried! After Janumet there was competitive bidding … a busy week, indeed!

stellar 2nd International Congress on Prediabetes and Metabolic Syndrome in Barcelona (April 25-28). The speaker lineup for this meeting (just like at the 1st International Congress on Prediabetes in 2005 in Berlin – write us for those notes if you like, as that was one of our favorite meetings ever) is extraordinary – see our conference preview below. We don't believe prediabetes has received as much attention as it deserves, though this conference may mark an important shift in emphasis toward diabetes prevention. On the note of prediabetes – check our featured lit review for the month, on the ADA recommendations on IFG/IGT published in March in Diabetes Care*. We found the recommendations to be conservative but understandable given the limited evidence base in this area. Last but not to be missed is technology maven Dr. David Klonoff's 3rd Annual Clinical Diabetes Technology Meeting in San Diego (April 20-21), where new technologies and therapeutics will be the big focus (www.clinicaldiabetestechnology.org).*

We're excited about publishing the third issue of* diaTribe*, our patient newsletter, earlier this week. *The newsletter has evolved over the last few issues as we've attracted more guest columnists. We're working hard to make* diaTribe *a useful resource for smart, intensively managed patients, and we love feedback, so please check us out at www.diatribe.us and tell us what you think! Our trademark feature, Learning Curve, describes the workings of Symlin and what we've learned about this sleeper drug since it came to market two years ago. This issue also has a fantastic Logbook, Jim Hirsch's column, on the transformation of insulin from a miracle drug in the 1920s to a feared and avoided therapy, unfairly we think. Also, with excitement for new products like Medtronic's MiniLink and LifeScan's UltraMini, it is clear that small continues to be sexy. In What We're Reading, Jim Hirsch writes about Amy Tenderich's "Know Your Numbers, Outlive Your Diabetes" – an incredibly useful book for any new patient. Finally, David Mendosa, a successful blogger and web-writer with type 2 diabetes, guest-writes an inspiring Test Drive on Byetta.*

—Kelly L. Close

MAJOR HEADLINES, DCU #67

In this issue:

Quotable Quotes from March's DCU:

Lars Sorensen, President and CEO, Novo Nordisk:

- *"Ideally we would like to cure diabetes, because that's what our customers, the people with diabetes, would really want. And since I cannot legitimately say it cannot be done, we should, as a pharmaceutical company, work at eradicating the disease, even though it would have some serious implications on our business. There are these scientific signs that it might indeed be possible. So it will be done at some point in time, and it might as well be us."*
- *"There has been, at least from our perspective, a revelation going on, where these political leaders can start to see that these chronic diseases . . . will become a huge burden unless we do something. And what we have to do is make a very long-term investment. It starts with education in schools, redesign of our cities – the whole redesign of our way of life.*
- *"With the general public, unfortunately, [pharmaceutical companies] are not held in very high standing. Unfortunately. But it's to a large extent our own doing. And I'm not saying Novo Nordisk, but the industry in general, and that's just something we need to recognize …"*

Quotable Quotes from the Wider World:

John Buse, MD, PhD, CDE, ADA President-Elect, in an MSNBC article by the Associated Press:

- *On Exubera: "I think Pfizer will wish they had never gotten into this. I doubt they'll regain their investment. There is no advantage to Exubera and there may be a safety risk. I see it as my job to talk people out of [using] it."*

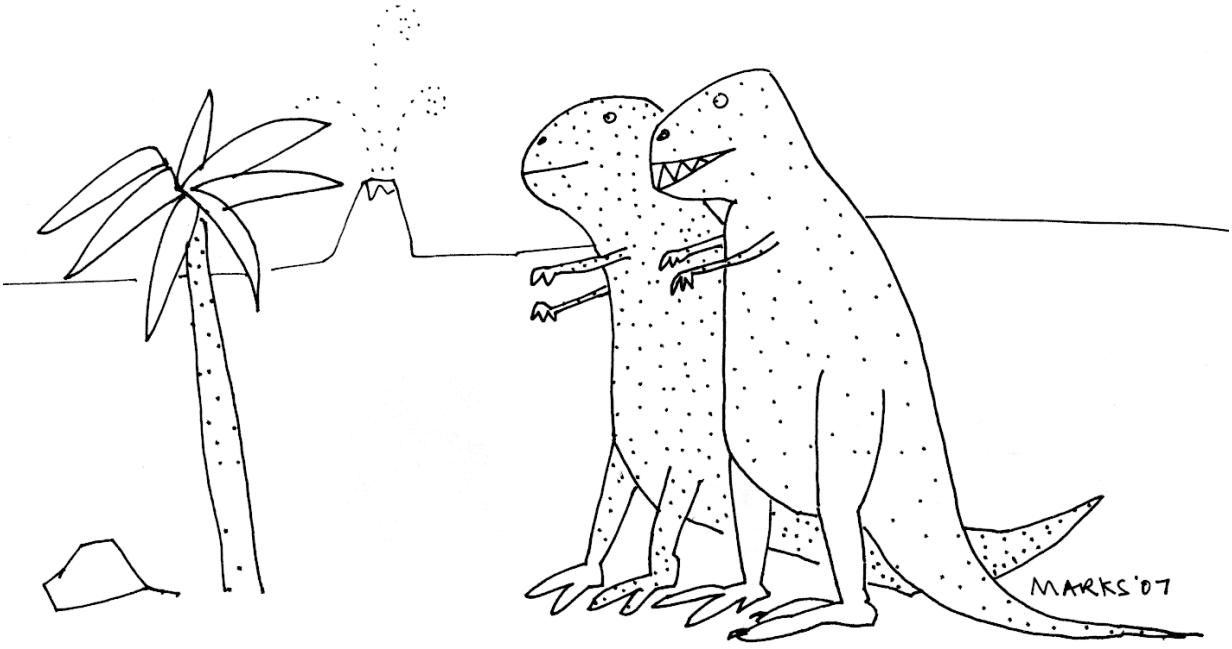
Prakash Deedwania, MD, UC San Francisco, Fresno, at American College of Cardiology meeting:

- *While co-chairing the "Great Debates in the Metabolic Syndrome" session: "Metabolic syndrome is the biggest controversy in the last year and a half..."*

Elizabeth Barrett-Connor, MD, UC San Diego, at American College of Cardiology meeting:

- *Arguing against rimonabant in the "Great Debates in the Metabolic Syndrome": "The largest risk for this drug… might be off-label for women who are a size 8 and want to be a size 2."*

diaTribe FingerSticks



"*You know, I find that an herbivore or two in the afternoon really evens out my glycemic variability.*"

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.

- March 28: Diabetic Furies: New ADA Leader Takes a Stand and Catches Hell
- March 23: John Edwards comparing diabetes and cancer?
- March 19: How a Worldwide Diabetes Epidemic Could Be A Good Investment Opportunity
- March 15: Clinton at the Global Changing Diabetes Leadership Forum
- March 5: Hand-off: a new kidney, a lost opportunity
- March 5: The pain of neglect: more aggressive intervention needed for type 2

Besides writing our own blog, we also write a new blog for Revolution Health called "Up Close and Personal" on life with diabetes. You can find it at www.revolutionhealth.com/blogs/kellyclose.

- March 28: Big Gulp: Sweet Drinks Sweep America
- March 28: The Diabetic Furies: New ADA Leader Takes a Stand and Catches Hell
- March 23: Carrying all the stuff is really a drag...
- March 12: Clinton to the Rescue? The Former President Weighs in on Diabetes

- March 9: Know Your Numbers, Outlive Your Diabetes - New Book on Diabetes Gives Patients an Excellent Framework for Their Care
- March 8: Symlin - yes or no!?
- March 5: Diet Pills May Offer More Hope Than Weight Loss – Fat Chance!

Coming soon in DCU…

- **Conference reports from ADA islet research symposium in Georgia, American College of Cardiology meeting in New Orleans, and Diabetes UK in Glasgow**

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

1. DCU Company Watch

- **MicroCHIPS—Equity investment led by Novartis Venture Fund**: MicroCHIPS announced April 3 that it has raised $13.4 million in a round of investment funding led by Novartis Venture Fund, whose Global Head Reinhard Ambros has now joined MicroCHIPS' board of directors. Another new investor, CSK Venture Capital of Japan, also contributed funding for this round. Other contributors include previous MicroCHIPS investors Polaris Venture Partners, IDG Ventures, Medtronic, Boston Scientific, Intersouth Partners, and Boston University Community Technology Fund. MicroCHIPS is developing implantable reservoir arrays that can hold either drugs or sensors. When implanted in patients' bodies, the devices can be wirelessly controlled to release drugs on demand or expose biosensors to the surrounding tissue for making measurements. Applications for the technology include treatments for diabetes, CVD, and osteoporosis.
- **Merck—FDA approves Janumet:** Merck announced April 2 that the FDA granted approval for Janumet. We see the timing as a big win for Merck, as it puts the Januvia franchise even further ahead of Novartis' Galvus, as long as drug safety continues to hold. The advantages of the combo are one co-pay and better efficacy; the downside is twice a day rather than once a day and possible sub-optimal dosing (everyone may not need the same dose of metformin!). More healthcare professionals certainly are calling for earlier, more aggressive *dual* initial therapy – we suspect the PCPs will be more in support than the endos because they have traditionally been more enthusiastic about combo drugs. Specialists are more likely to prefer titrating drugs (that need it) separately and thus less likely to go to Janumet directly than to first optimize metformin, then add other drugs, etc… and they also tend to see more complicated patients. Merck has executed well in the primary care market already, and the company has done a very good job of launching Januvia, so we expect the same when it comes to Janumet, particularly as there will be no pricing pressure: Merck has priced Janumet at $4.86/day, *exactly* the same as Januvia. Merck will also benefit from a few other things, namely: 1) we assume it can argue the FDA isn't worried about a class effect with the skin lesions that have slowed Galvus; 2) the efficacy does seem to look better in combination with metformin, and although there are lots of ways to argue about the trials, we do hear from doctors that the drugs work better together. 3) PCPs are also an easier audience for the sales reps to target because they're less likely to know (and probably care, as long as Janumet is approved) about safety concerns with a competitive drug and thus worry about any potential safety issues that may have prompted the FDA to give Novartis the approvable letter in November and the second delay in February. On the negative side, we assume much (all?) of managed care will want patients to try metformin alone at the start. Last, this is also a win for Merck as it comes on the heels of the EU approval for Januvia, where the company has said it will launch soon in several European countries. We are eager to watch the incretin "test" in Europe – stay tuned, we think it looks better than many may imagine.
- **Aradigm 4Q06—Novo Nordisk's AERx iDMS continues on track in phase 3 studies**: In Aradigm's March 29 call, CEO Igor Gonda gave an update on AERx iDMS inhaled insulin, for which Novo Nordisk currently has full developmental responsibilities. The device is in phase 3, with six ongoing trials comparing the product to oral anti-hyperglycemic agents and injections in about 3,000 type 1 and type 2 patients. The company looks for the product to launch in 2010. Novo is currently also developing a second-generation product, which will be lighter and smaller. Gonda said one of AERx iDMS's competitive features is the ability to dial in insulin units for dosing—we understand that AERx iDMS will have the smallest titration increment among the inhaled insulins, which is terrific for type 1 patients and intensively managed type 2 patients, though we don't see these as the early adopters of inhaled insulin (or probably adopters at all). That said, if demand grows for inhaled insulin, then all else being equal, single unit dosing is definitely an important advantage. The device also reminds the user how to breathe correctly each time it is in use. Aradigm and Novo remain under

a technology transfer agreement for the AERx needle-free technology. Novo holds the rights to developing products for glucose control, but Aradigm can develop AERx for other markets. In Q&A, Gonda noted, interestingly, that one of Novo's key focuses in phase 3 will be to compare the product against TZDs, which he thinks could help with reimbursement. The target is obviously type 2s who are delaying insulin to be on orals. Pfizer has done some smaller studies in that area with Exubera.

- **Medtronic—Diabetes awareness survey for American Diabetes Alert Day**: March 27 marked the ADA's 19th annual American Diabetes Alert Day, when the organization encourages people to promote diabetes awareness among friends and colleagues. In honor of the event, Medtronic put out an excellent press release on a survey on diabetes awareness. Medtronic surveyed ~ 2,500 adults at the start of March and asked four questions to get at the following issues: 1) How many types of diabetes are believed to exist; 2) How widespread is the belief is that only children can be diagnosed with type 1 diabetes; 3) Which of several statements about the differences between type 1 and type 2 are believed to be most accurate; and 4) How those living with type 1 diabetes can cure their illness. They found the following, all of which reinforced a real lack of awareness about diabetes, especially type 1 diabetes: 1) 78 percent of those polled did *not* know the difference between type 1 and type 2 diabetes; 2) 67 percent of the population mistakenly believed there is a cure for type 1 diabetes (25% believed that a proper diet would cure it, 16% perceived insulin as a cure, and 18% thought that losing weight would be a cure; 3) only 51 percent knew that there were two types of diabetes; and 4) only 22 percent of US adults believe that type 1 patients produce no insulin. This reinforces, of course, the awareness problems evident globally – we think it's great that Medtronic is highlighting this in the diabetes community.
- **Medtronic—REAL Diabetes Control Website launched**: Too, Medtronic launched a new website on March 27, concurrently with the ADA's American Diabetes Alert Day. They characterize the site, www.RealDiabetesControl.com, as a place "patients can access information about the latest treatment options to improve their diabetes control." We think the site clearly improves the company's online marketing to diabetic patients. The site conveys the messages of empowerment and less hassle, captured by the surfer's quote: "Because I have better control of my blood sugar overall, I don't have to come in nearly as often." Each page of the site offers a link to sign up for an e-newsletter, which promises to send information on the "benefits of real diabetes control" or an unspecified event in your area. The site is stylish and generic at the same time. It's easy to read, beautiful to look at, but avoids promoting one product over another. Each therapeutic option gets its own page. The page for "insulin pump therapy" enumerates both the advantages ("imitates body's natural functions," "one 'injection' every three days," etc.) and the disadvantages ("4-6 finger sticks a day," "increased risk of DKA," etc.). By and large, we found it a fairly balanced assessment of different treatments. Patients will appreciate (for the most part) the absence of hype. That said, the link to "real-time continuous glucose monitoring" describes it as a "revolutionary new tool" without identifying any of the tool's shortcomings (accuracy, false alarms, etc.). In short, we believe the site's handsome design and message of education and empowerment will serve Medtronic well in its efforts to reach patients directly through e-newsletters or special events. We suspect we'll see more of this from other companies as direct consumer marketing gains traction in the diabetes world - we know these aren't new per *se* – it's just that we are seeing more directed and focused sites, which we think is terrific for patients.
- **Conjuchem—Poor phase 1/2 data presented in muted call**: Conjuchem hosted a call on March 27 to discuss results from a phase 1/2 study of its albumin-conjugated GLP-1 product, PC-DAC:Exendin-4. In our view, the data were mixed. First, the treated groups had no weight loss, which management attributed to the short length of the trial. We note, however, that the company had announced weight loss from a 3-week trial in 2006, a conflict hard to resolve. Second, there was no significant post-prandial improvement, though the company talked about "more analysis." Instead, the focus was on fasting blood glucose, which we continue to view as a poor measure for reporting

glycemic control since so many things can affect fasting, and the mostly single-digit percentage declines Conjuchem reported could well have been a result of a number of things beyond the drug itself. The side effect profile showed about 20% nausea and higher vomiting in the highest-dose group (3 mg). We would think that vomiting is a huge detractor without weight loss as a tradeoff. Management spoke only of severe hypo rates (none) but didn't mention mild to moderate hypoglycemia, so we wouldn't be surprised if there had been some. Lastly, the company didn't say how many patients got to goal, explaining that it hasn't done this analysis yet, which was surprising to us since it seems a pretty straightforward. Management said that it will be pressing on with the phase 2 study, which will be a metformin add-on trial, testing 2-3 doses, 30 patients per cohort, in a 3-month study**.**

- **Merck—EU approval for sitagliptin granted**: Sitagliptin was approved (brand name Januvia in some venues, Xelevia in others) in the EU on March 26. The label sounds similar to that in the US, with assessment of renal function recommended at initiation and periodically (no requirements). Merck apparently only filed for add-on to metformin and/or TZD, not add-on to sulfonylurea, which is interesting because the company is pursuing the latter indication in the US now. We note that TZDs are used far more rarely in Europe than in the US, but metformin prescriptions are very common. We understand that tolerability issues aside, the cost of TZDs is a major barrier to getting the drug covered, so it will be interesting to see how sitagliptin does in comparison. We note that Merck made a major push at Diabetes UK on incretins, though they have not yet been approved.
- **Sanofi—FDA panel meeting set for June 13 for rimonabant**: Sanofi announced on March 26 that the FDA's endocrinologic and metabolic drugs' advisory committee will be meeting on June 13 to discuss rimonabant's safety and efficacy in preparation for the July decision. We think this will be an incredibly interesting meeting, and this is an excellent example of a meeting that *should* happen – there should be a meeting with obesity specialists, endocrinologists, psychiatrists, psychologists, etc. to discuss this drug that clearly has some real positives for some patients and clearly has some big questions associated with the side effect profile. The decision will come on the heels of the announcement that committees can't include any doctors who have received more than $50,000 from the company being evaluated. While it might sound like a positive – doctors will be able to deliver more unbiased feedback – we believe the rule is an unqualified negative because of the risk that panel members will not be as knowledgeable. In our view, the doctors who are compensated by the company for clinical trials, etc., are the ones most likely to understand the products.
- **DiObex—Good phase 2a results for oral anti-cortisol type 2 drug**: DiObex announced positive results on March 26 from phase 2a studies with DIO-902, its oral once-daily drug candidate for type 2 diabetes. DIO-902 inhibits synthesis of the stress hormone cortisol. Data from various epidemiological and clinical studies have suggested that a link exists between high cortisol levels and adiposity, insulin resistance, and hyperglycemia—some of the common elements of the metabolic syndrome and type 2 diabetes. The two-week trial with DIO-902 included patients with type 2 diabetes who were randomized to placebo or three different doses of the drug. Patients who received DIO-902 had drops in total and LDL cholesterol as well as modest drops in A1c from fairly low mean baselines values, generally between 7% and 9%. Few side effects were observed *per se*, but there is a potential for drug-drug interactions because DIO-902 is a purified enantiomer of racemic ketoconazole[2], a drug used to treat fungal infections, which does have drug-drug interactions with a subset of statins and a number of other marketed drugs. We understand that DIO-902 is supposed to be cleaner than ketoconazole, but much work in the area needs to be done. Daniel Green, President of DiObex, told us that he expects if everything goes well, the drug could enter phase 3 by early 2009

[2] A racemic drug is actually a mixture of two molecules (enantiomers) that are mirror images of each other, much like your left and right hand. DIO-902 represents a purified version of only one of ketoconazole's enantiomers. The two enantiomers of a drug will frequently have different effects – one may be inactive while the other is active, but sometimes one may actually be toxic while the other has a beneficial effect. This is why purified enantiomers are sometimes safer than racemic mixtures.

and could be submitted by the end of 2011. For now, the company intends to do more work before looking at partnering options. It will start enrolling patients in a 16-week phase 2b dose-ranging study in mid-2007. While this is early work, we think DIO-902 could potentially be a good combo drug because of its novel mechanism. DiObex has another drug (DIO-901) in the pipeline. It is called VLD-Glucagon (very low dose glucagon) and is intended for the prophylactic treatment of hypoglycemia in patients undergoing insulin intensification. Green said that DiObex is developing some attractive formulations of the product for subcutaneous injection and plan to enter initial human trials with it toward the end of the year. In other great news for DiObex, the company will have two abstracts presented at ADA - Dr. Steve Edelman will be presenting an abstract on DIO-901 and Dr. Sherwyn Schwartz will be presenting an abstract on DIO-902 – we very much look forward to learning more.

- **Animas—Animas 2020 insulin pump launched; flat screen supplies "Wow!" factor**: Animas announced March 21 that it would be launching its 2020 pump, which will replace the previously forthcoming IR1275. We would say that the three most notable features of the new pump are: 1) It's now the smallest traditional pump on the market; 2) It has a backlit organic light-emitting diode (OLED) screen, which is supposed to deliver brighter and clearer images than traditional pump screens – it's definitely easier on the eyes; and 3) Precision of dosing; the minimum adjustment increment will be 0.025 U/hr. We think these features could be particularly helpful for young children or anyone who is highly sensitive to insulin, and the new improvements on the display screen will benefit folks with decreased vision. The pump will have many of the usual bells and whistles: a 500 food database, waterproof at 12 feet for 24 hours, and storage memory for BG and carb values.
- **Sanofi—SoloStar insulin pen to launch in Europe**: Sanofi-Aventis announced March 21 that it will launch the disposable SoloStar pen in Germany in April, France in May, and other countries across Europe over the next 12 months. SoloStar pens were approved in Europe in September of 2006 but are still under review at the FDA in the US. The pens will contain Sanofi's long-acting insulin analog glargine (Lantus) and rapid-acting insulin analog glulisine (Apidra). It will be a coup for Sanofi if this pen is user-friendly, as its current pens aren't considered premium. Sanofi will position the SoloStar as "easy to use, easy to inject and easy to teach" – in particular, it's emphasizing the pen's drive mechanism, which will require less injection force than competitive pens. The dose range will be up to 80 units and can be adjusted in one-unit increments, which is comparable to any disposable pen. No word yet on pricing.
- **SpectRx—Intent to sell SimpleChoice insulin infusion set business:** SpectRx announced March 20 that it has signed a binding agreement for its SimpleChoice insulin pump set business, as well as a nonbinding intent-to-sell letter for the business. The deal was made with an undisclosed party interested in buying or licensing the SimpleChoice product portfolio. The portfolio includes non-core parts such as disposable infusion sets and insulin reservoirs. SpectRx expects a transaction to be finalized sometime in 2007. We are eager to find out more financial details but aren't yet aware of any.
- **Amylin—Delta Burke and Virginia Valentine in DTC campaign**: Delta Burke, an actress with type 2 diabetes, is the face of the "Let's Talk" initiative for Byetta, a direct-to-consumer campaign from the product's manufacturers, Amylin and Lilly. Launched on St. Patrick's Day at the New England Spring Flower Show in Boston, the campaign will visit 10 cities by August. Burke will be accompanied by Virginia Valentine, the well-known and very high regarded CDE hailing from New Mexico; Chris Smith, The Diabetic Chef; and Nikki Kimbrough, a fitness trainer from Bally Total Fitness. We think this is a promising campaign – the celebrities are going to *excellent* events – and trying to meet people directly with type 2 is wise. The campaign seems designed more for women than for men; we like that it will be done with diet and exercise experts – very responsible.

- **Amylin/Lilly—Diabetes UK is the "Byetta meeting:"** Diabetes UK was an exciting meeting for Lilly and Byetta; at least in the UK, Byetta is being paid for at present (68.24 pounds per month, a little more than half the US price of $248 per month for a 10 mcg pen) and we assume NICE will weigh in at some later point. At the same cost for 5 mg and 10 mg pens, no patients will be disgruntled about paying more. It sounded like there would be an official NICE decision next year, but for now, excitement mounts about the UK launch on May 1 and other launches in Spain, Italy, and France in 2007, following price negotiations. Timing wasn't yet available, but the press release does say the launch in EU countries will be "shortly." Given how Merck executed such a fast launch for Januvia in the US, it will be interesting to see how fast Lilly will launch Byetta in Europe by comparison, although it's not an apples to apples comparison because Merck will likely again go after more primary care doctors first.
- **Home Diagnostics 4Q06—Continuing to gain ground in managed care**: CEO Dick Damron discussed HDI's quarter and year in a stimulating March 13 call – HDI certainly is on a roll. In managed care, HDI gained inclusion on five new formularies, two of which as an exclusive provider and one as a sole provider – big wins. This quarter HDI launched TRUEread, a BGM product targeted at Medicare/Medicaid populations. In 2008, the company expects to launch TrueResult (formerly Resolve), with auto-calibration and a "shorter test time and smaller sample." Approval and subsequent launch of new data management software TrackRecord are expected in 2Q07. In retail and distribution, the price will increase (as announced last year), for TrueTrack test strips, effective April 1. In litigation, HDI announced that the district court ruled in favor of HDI in the patent infringement suit brought by Roche, which went to trial in February of 2007. HDI's net income of $12.3 million exceeded guidance of $11-12 million. Revenue for 4Q was just under $27 million, in keeping with full year 2006 guidance from last quarter. The revenue from its mail-service channel was down year-over-year but up sequentially 24%. The domestic distribution revenue was disappointing due, management said, to a seasonally strong 3Q. Revenue for 2007 is expected to be $126 to $130 million, with more expected at the back end.
- **Medtronic—REAL-Time CGM approved for pediatric patients**: Medtronic received pediatric approval on March 12 for continuous monitoring for kids and teens ages seven to seventeen. Medtronic indicates that its Guardian and Paradigm REAL-Time systems will be available in specific pediatric models. This is long awaited and a definite positive. The timing with the approval of the smaller MiniLink last month is also a big positive for the company as size is very important, given body image issues with pumps and sensors – the new transmitter is a third the size of the last generation. The Guardian RT was being shown at Diabetes UK, but the launch date isn't until later this year. On the upside, the form factor on the newest RT looked quite slick when we saw it at Dr. Steve Edelman's fabulous Taking Control of Your Diabetes Meeting last December. We've not heard much on the most important aspect of any new combination product – the quality of the sensor. On sensors more broadly, Medtronic will have new competition when DexCom's 7-day sensor is approved. We expect in terms of convenience, this will be a positive but believe there will be patient backlash on price - if there is a more robust shut off than on the 3-day sensor, then most patients will have to pay effectively a higher daily price and there is resistance to this.
- **Novo Nordisk—Dr. Alan Moses appointed Chief Medical Officer:** Novo Nordisk announced March 12 that the highly respected Dr. Alan Moses, who has been with the company since 2004, has been appointed Chief Medical Officer of the North American division. We note (once again) that the company is extremely focused when it comes to recruiting and promoting top talent – they have been extremely successful in this regard and they show no signs of stopping. To have Dr. Moses' brainpower and critical patient understanding and insights at the very top is a real win indeed – for the company as well as for patients. Dr. Moses was the senior vice president and chief medical officer at the Joslin Diabetes Center before joining Novo Nordisk and his understanding of the patient perspective is renowned.

- **Takeda—Pioglitazone linked to increased risk of fractures**: The FDA issued a notice on March 9 that Takeda was sending letters to notify healthcare professionals about an increase in fractures in female patients taking pioglitazone. As a reminder, the fracture issue was first seen in the ADOPT trial results with rosiglitazone, GSK's TZD, where the incidence was about 2.2 per 100 patient-years. Subsequently, the FDA asked Takeda to look at its clinical trials data again, and the company found that there was an increase in fractures for pioglitazone as well, at a rate of about 1.9 per 100 patient-years compared to 1.1 per 100 patient-years for placebo. We heard from Takeda that the reason this wasn't noticed before was that the rate was low enough that it wasn't statistically significant in the pooled male and female data. The mechanism for this side effect is not yet known – the fractures have been observed mostly in the distal upper limb and lower foot (i.e. forearm, wrist, and hand and tibia, fibula, ankle, and foot), and GSK at least has claimed that it is not an osteoporosis issue. With this new notice, we note that TZDs may be hitting a rough point – prescription trends for the rest of the first quarter and the second quarter of 2007 will tell.
- **Conjuchem 1Q07—Little news, trial results continue to show weak efficacy:** Conjuchem announced its 1Q07 results on March 8; it ended the quarter with a net loss of $18.6 million, compared with a $10 million loss a year ago. This increase stemmed from a large increase in R&D expenses of $9.5 million, due largely to purchase of raw materials for the manufacturing of its albumin-conjugated GLP-1 product, PC-DAC:Exendin-4 or CJC-1134-PC. The company said this would be enough to satisfy the rest of its needs for 2007, including phase 2 trials and toxicity studies that would enable phase 3. From over $110 million in cash at the end of 2006, Conjuchem now has $54.9 million in cash and working capital of $39.1 million. The guidance above expanded only slightly on the guidance from its last update – this announcement had very little new information. In its press release at the end of January, the company mentioned promising phase 1/2 single-dose trial results for both tolerability and efficacy (with weight loss as well as glycemic control) – we think this had been a little optimistic given results of the recent call. We question the trial design and what constitutes efficacy. ConjuChem also has a very-long-acting insulin (PC-DAC:Insulin) based on the same technology that is in early stage development; the release did not discuss this in any depth. We believe the company continues to lack credibility not just among investors but also among HCPs.
- **Metabasis 4Q06—Phase 2 studies for two gluconeogenesis inhibitors ongoing:** Management reported at its March 8 call that top line results from the phase 2b trial of CS-917, the company's gluconeogenesis inhibitor in co-development with Daichi Sankyo, are expected in mid-2007. The compound should be poised for phase 3 at the end of the year. CS-917 is an inhibitor of FBPase, an essential enzyme for gluconeogenesis in the liver. The drug works by decreasing gluconeogenesis and thus reducing liver glucose output. Metabasis independently developed a second-generation gluconeogenesis inhibitor, MB07803, and will move into phase 2 toward the end of March or early April. Also in the pipeline, Metabasis entered a collaboration agreement with Merck last year to develop AMP-activated protein kinase (AMPK) for use in type 2 diabetes, hyperlipidemia, and possibly obesity. Metabasis received $1.8 million from Merck in 2006 for this agreement, and we're very eager to hear more about it.
- **Nastech 4Q06—Phase 2 plans for intranasal insulin & PYY despite Merck withdrawal:** Nastech announced in its March 7 call that it plans to initiate phase 2 trials for both intranasal insulin and intranasal PYY_{3-36} (for obesity) in 2H07. CEO Steven Quay said that phase 1 pharmacokinetic studies of the intranasal insulin showed that it has faster time-to-peak (16 to 19 minutes) than rapid-acting Novolog and greater bioavailability than Exubera. The company believes intranasal insulin would be competitive and priced the potential sales at $1.5 billion per year, which we find overly optimistic in light of Exubera's poor performance to date. Quay spent some time discussing Merck's intranasal PYY study from last year, which showed a placebo-subtracted weight loss of only 0.9 kg over 12 weeks and caused Merck to drop the PYY program (Merck had been looking for a placebo-subtracted weight loss of 2.1 kg). Quay pointed out, however, that there was a divergence between treatment and

placebo arms in the study, and that even the placebo arm lost 2.8 kg. Also, both groups lost 5 kg in the two-week run-in period prior to the start of the trial. He reiterated that Nastech's phase 1 studies looked good and noted several differences in Nastech's phase 2 study design that he believes will make it more successful: the study will go for six months rather than three, and it is hoped that the PYY and placebo curves will continue to diverge given the longer duration. Nastech's study will enroll nearly double the number of patients enrolled in each of Merck's test groups and will try to prevent more dropouts. Nastech will also abandon Merck's "sink or swim" approach to dosing, where patients were immediately dropped if they could not tolerate a given dose. From our point of view, the Merck study was extremely discouraging, and if there is an efficacy problem, we're not sure Nastech's adjustments will really solve it.

- **DexCom—Sixty million dollars in convertible senior notes priced:** DexCom issued notices on March 6 and 7 that it had priced $60 million in convertible senior notes in a private offering to institutional buyers. We reference that management reported in the 4Q06 call that DexCom had around $55 million in the bank. With prospects of losing about that much in 2007, concerns mounted about its cash needs, so the funding is definitely a sigh of relief near term. DexCom also celebrated the one-year anniversary of its sensor approval in late March – although the market has clearly experienced troubling quality and reliability issues in its first year, we do believe that if reimbursement eventually comes (~2009), we'll look back at this troubling period and think that the 2010 generation sensors and the progress on open-loop technology really benefited from these early days – they will have stood on the shoulders of the early ones.
- **Innodia—Talking with CEO Dr. Claude Vezeau about the obesity drug Adyvia:** Two new members joined Innodia's scientific advisory board in March: Dr. David York, Director of the Center for Advanced Nutrition at Utah State University, and Dr. Robert Zamboni, a former Merck executive. Already on the board were Dr. Harold Lebovitz and Dr. Gordon Weir, both very well respected. We spoke with CEO Dr. Claude Vezeau about the company's pipeline. Adyvia, an oral drug for obesity in phase 2 studies, is Innodia's only product currently in clinical trials. It increases energy expenditure and satiety and thus "mimics exercise," which to us sounds a little too good to be true. Dr. Vezeau explained that while other anti-obesity drugs act on the central nervous system (Sanofi's rimonabant and Abbott's Meridia, for example), Adyvia has a peripheral center of action. Dr. Vezeau expressed some skepticism toward rimonabant, saying that drugs for obesity cannot "make healthy subjects sick" with their side effects. He emphasized Adyvia's clean side effect profile as a major advantage; it is too early to assess that but we will be eager to follow. Currently, phase 2 studies involving about 100 obese patients are half-enrolled, and results are expected at the end of 2007 with dose ranging phase 2 studies to follow. Dr. Vezeau projected that phase 3 would start in early 2009. The current strategy is to partner Adyvia, which is also helpful in type 2 diabetes. Partnering would "ideally" be in 2008. Innodia also has a few preclinical compounds in research. One is a next-generation to Adyvia, which will be developed with more focus on type 2 diabetes. In addition to weight loss, it is supposed to have a direct effect on A1c. The other is an anti-amyloid; 90% of type 2 patients have amyloid deposits in their islets, which are hypothesized to contribute to decreased beta cell function and mass. Proof of concept should be in the next two months. Management expects both of these programs to reach the clinic in the next couple of years, and we'll be interested to watch developments.
- **Transition Therapeutics—Early phase 2 data for potential islet neogenesis therapy:** CEO Tony Cruz hosted a conference call on March 5 to discuss interim safety and tolerability results from an exploratory phase 2a trial for E1-I.N.T. (Islet Neogenesis Therapy), a combination of selective growth factor E1 and gastrin intended to stimulate regeneration of beta cells that Transition is developing in collaboration with Novo Nordisk. This trial included 30 insulin-treated type 2 patients who were treated for 28 days and then followed-up for six months. Data from the first three months suggest that tolerability may be an issue. There was a high dropout rate (six out of 20) due to adverse events as

severe as vomiting, but as with other nausea-inducing drugs (like Byetta), slow and systematic escalation helped improve tolerability. A1c dropped 0.97% from baseline by month two post-treatment and 1.12% by month three—baseline is unclear but over 7%, certainly. Cruz noted that glucose tolerance, insulin secretion, and insulin to glucose ratio also showed positive trends. Novo Nordisk holds exclusive rights to E1-I.N.T., and the company will have to decide whether it wants to move forward with it by around August. Meanwhile, Transition is moving forward designing a larger phase 2 trial to optimize dosing without a final decision from Novo; Cruz indicated the company will be pursuing both type 1 and type 2 indications. It is also moving forward with generation two and three of its gastrin-based treatments, gastrin in combination with GLP-1 and DPP-4, respectively. Transition will be looking to partner with companies that have formulations of these drugs.

- **Wellpoint—Health care insurer to offer free meters**: Wellpoint, Inc. provides health insurance to 34 million Americans and is the nation's leading health plan provider. The company announced February 27 that it will be offering free blood glucose meters to members with diabetes who require blood sugar monitoring, as determined by their physicians. The four meters that will be offered under Wellpoint's plans are LifeScan's OneTouch Ultra and Ultra2 and Roche's Accu-Chek Aviva and Compact. We're encouraged to see a provider promote SMBG and think that free meters are an excellent first step, but we note that equally strong reimbursement for test strips and diabetes education is going to be even more essential for successful SMBG. We've often heard HCPs say that reimbursement for phone calls and emails might actually put fewer burdens on the system because it would improve preventative care and help reduce the need for more expensive services to treat complications; we think it would be amazing to see managed care take a leading role here.
- **OptiScan—OptiScanner study results presented at SCCM Critical Care Congress**: OptiScan presented a poster of results from a validation study of OptiScanner, its point-of-care glucose and lactate monitor, at the SCCM Critical Care Congress from February 18-21 in Orlando. OptiScanner is intended for hospital bedside use; it automatically draws samples every 15 minutes from existing vascular lines for a total of 96 measurements daily requiring 9.6 mL of blood in all. The device uses IR spectroscopy readings to measure blood plasma glucose and lactate, which frees it from potential lag issues that interstitial and noninvasive monitors may have. Also importantly for accuracy, it is programmed to take into account spectroscopic interference from some 200 endogenous blood plasma substances and drugs. The study reported in the poster took place from February to May 2006 at Stamford Hospital and included 86 Intensive Care Unit patients and 16 Intermediate Care Unit patients, from which 292 samples were drawn. The samples contained 194 different drug substances; these did not interfere with the accuracy of the glucose and lactate measurements. The r^2 correlation between OptiScanner and reference measurements was 0.93 for both glucose and lactate. All in all, we think the accuracy findings and lack of interference from circulating drugs is promising; this will be important for an inpatient product. The George Institute is currently conducting a large inpatient trial called NICE-SUGAR (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Evaluation) involving some 5,000 patients to look at whether an insulin infusion regimen to maintain glucose at 4.5 to 6.0 mmol/L (80 to 110 mg/dl) vs. 8.0 to 10.0 mmol/L (140 to 180 mg/dl) makes a difference in 90-day mortality in intensive care patients who upon admission to the hospital are predicted to stay in the ICU for at least one full day. Dr. Greet Van den Berghe's studies have suggested that there should be a benefit – we note that a positive result for intensive glucose management would certainly move the evidence forward for intensive insulin infusion (and accordingly intensive glucose monitoring) in the ICU. We look very forward to the results.

—by Daniel A. Belkin, Jenny J. Jin, and Kelly L. Close

2. Marching Toward A Billion: Novo Nordisk's Diabetes Forum Presents Global Challenge

One month before Bill Clinton was inaugurated as president, his campaign chairman from his first political race – for the House of Representatives in 1974 – died from diabetic complications. So Clinton, while he was in the White House, understood the seriousness of the disease, but he now says he all but ignored it.

"I thought we were doing okay, but it turns out we did nothing," he said. "You should always assume that even a diligent president gets stuff wrong."

Clinton's surprising acknowledgement came during his keynote address last month at the Global Changing Diabetes Leadership Forum in New York. His comments highlighted a central message from the two-day event: that diabetes, for all its devastation, for all its skyrocketing numbers, still escapes notice. "Get the facts out," Clinton said. "Our enemy here is ignorance."

The Forum, sponsored by Novo Nordisk, brought together the international glitterati of diabetes – 185 government and business leaders, health care professionals, social scientists and patient advocates. Twenty countries were represented.

Novo Nordisk Chief Executive Officer Lars Rebien Sorensen opened the meeting with a grim projection. He estimated that 550 million people worldwide currently have diabetes or pre-diabetes, but in 20 years, he expects that number to reach one billion – certainly a bleaker projection than we have previously heard[3]. No longer is Novo Nordisk calling the crisis an "epidemic." It is now a "pandemic," and unless its scope is recognized, Sorensen said, "Hell will be upon us."

In an interview with us in late March, Sorensen acknowledged that he came to the Forum apprehensive about its merit – "I wondered if this was just going to be another meeting" – but left encouraged by its international scope and by the prominence of its attendees. Topping the list was former president Clinton, who tentatively agreed to support diabetes awareness through his foundation.

How vigorously remains to be seen, but what is certain is that he understands the problem and that he can mobilize and inspire a crowd like few others. He received a raucous ovation from attendees when he stepped to a microphone in the crowded room at the Jumeirah Essex House. His hair is now white but he looked lean and fit, and he's not lost that famed roguish charisma – that ability to connect with a room full of strangers – that served him so well as a politician. The audience was rapt as he spoke, most heads leaned forward.

In this case, Clinton discussed his own fragile health in a way that was directly relevant to type 2 diabetes. He conceded that he was "always overweight," adding, "For most of my adult life, I ran 20 to 25 miles a week, but I ate wrong." His dietary sins finally caught up with him a couple of years ago, when he had heart problems and underwent bypass surgery. Modern medicine saved him. "I lived through something that would have killed 95 percent of the people in my condition 50 years ago," Clinton said. "Every day of my life I think of as an accidental gift."

Long out of office, Bill Clinton still feels our pain. Which is good, because he is less likely to blame diabetic patients for bad outcomes and more likely to encourage government intervention to improve care. For example, he praised current Arkansas Governor Mike Huckabee (and Republican candidate for president) for mandating that schools include every child's body mass index on his or her report card, and

[3] We agree, and are always confounded by the projections that never seem to add up. For example, in North America, even the International Diabetes Federation says that as of 2007, we have 28 million diagnosed and undiagnosed with diabetes, and the forecast is 41 million in 2025 – that's 18 years and we are said to be adding 1 – 1.5 million diagnosed in the US alone each year so by our math, just adding the low end of US diagnosed, we come to 46 million. While we hardly want to quibble about math, we do think there is a danger in underestimates. We think it's early to assume slowing growth and applaud calling a spade a spade.

he understands the grim social costs of poor health. "Eating wrong and no exercise – that's a slow death and much more expensive for society," he said.

Clinton said that politicians often miss profound societal changes because by necessity public officials are more focused on "headlines than trend lines," which was why he missed the soaring rates of type 2 diabetes when he was in office. Those rates, of course, will continue to increase globally, a byproduct of rising levels of industrialization and affluence, which has diminished physical activity, harmed diets, and increased obesity.

Several Forum panelists, during a "Socratic dialogue" moderated by Harvard Law Professor Arthur Miller elaborated on that point. Professor David Matthews, chairman for the Oxford Centre for Diabetes, Endocrinology and Metabolism, said that in urban areas around the world, 20 percent of the population is expected to have diabetes – rates that are already seen in Oman and Sri Lanka. "The rate will be so high that there won't be a single person on the planet who won't somehow be affected," Professor Matthews said. Dr. V. Mohan, president and director of Madras Diabetes Research Foundation in Chennai, India, was even more pessimistic, saying that for older people in some parts of the world, the rates could be 33 percent or even 50 percent.

The picture is bleak, but not hopeless. Professor Matthews also talked about several concrete ways to address the epidemic, including investing in research to find cures for both type 1 and type 2 diabetes, engaging all stakeholders to collaborate on a solution (e.g. the government could enforce calorie labeling and the food industry could sell healthier foods), subsidizing specialized care, continuing to raise media awareness, and educating governments about the economic consequences of poor diabetes care.

The fact that author Malcolm Gladwell was invited to join the panel seemed to confirm the obvious: diabetes is reaching the "Tipping Point." In a sobering aside, Gladwell suggested to the audience that we are moving to a time that, in the coming decades, the "new discrimination" in the U.S. will be centered on healthcare – who has what disease, who isn't covered, etc. If true, that's none too comforting for the diabetes community.

One of the themes emerging from the Forum's international participants in particular was that good healthcare should not merely be a privilege but a right, which is relevant to diabetic patients everywhere. Even in wealthy countries, many of those patients receive poor care – and for some, *no* care. Panel members cited familiar problems with the healthcare system, at least in the U.S., but they are worth reiterating. Why don't patients do better?

- Inefficient healthcare systems, not supported technologically, focus more on the bottom line than on providing research-proven therapies for disease prevention and treatment. Federal funding for prevention is critical – both for prevention of diabetes and of complications – but the already paltry sum of dollars spent on prevention is actually declining in real dollar terms, according to Novo Nordisk Chief Medical Officer Dr. Alan Moses. Considering the burden of disease, this is embarrassing.
- Healthcare organizations create narrow and sector-specific attempts to solve complex and interrelated problems that are better solved through collaboration and coordination. There is the need for a clear roadmap for the detection and treatment of diabetes and prevention of complications.
- Lack of alignment among different government agencies. We were a little skeptical at first – how hard could this be? But then we learned that the World Bank recently identified seven diabetes treatments that would save money throughout the world if prescribed, even in developing countries. They included, among others, glycemic treatment when A1c is over 9%, (over 9%!), blood pressure treatment when blood pressure exceeds 160/90, foot care in high-risk feet, preconception care (i.e., preparing for pregnancy, rather than starting pregnancy with A1cs above 9%-10%, to say nothing of 6%-7%), and prophylactic aspirin. Jonathan Betz Brown, Chair of the IDF Task Force on Diabetes

Health Economics, said that it is tragic that these treatments are not used more, but the opportunity for improvement exists. His words stuck with us, and what we found most amazing is how easy it is to be stuck in a US-centered, insured bubble - we had never even heard the announcement about this program – and we try to follow diabetes 24/7. Clearly, we're not as aligned as we think we are – this was real inspiration to us in terms of how we follow the field, that's for certain.

- Pharmaceutical companies all too often chase the next new medical solution rather than introducing effective treatments to wider audiences. While in some ways, we felt this was just the obligatory snipe at Big Pharma (which we think overall is doing an especially respectable job in diabetes), we certainly liked the idea of introspection. Unfortunately, we're not sure that this will happen where it most needs to.
- Food companies have the capacity to bring low-cost, healthy foods to the public, but instead they bring food packed with hidden sugar, salt and fat that are marketed to children and the poor. Children in particular are bombarded with the marketing of unhealthy foods and inappropriate role models.
- Politicians are more interested in quick fixes than long-term solutions.
- Disjointed insurance agencies don't share data, and certainly do not pay for preventive care, which means that the overwhelming majority of providers don't have the resources to educate patients or to start or train them on BG monitoring (for almost all patients) or insulin
- The patients who don't have insurance are in the lower socioeconomic group – often the population that suffers the greatest burden in diabetes. At the same time, there are increasing numbers of uninsured in the US, and, as a new trend here, we are now seeing people lose Medicaid coverage. Think about that – losing *Medicaid* coverage. Being so poor to need Medicaid coverage and then losing it. Finally, a great frustration in diabetes today is that the disease is concentrated in populations that don't have access to care (or have the least access to care).

There is, of course, no silver bullet to a pandemic, no quick fixes; only a relentless, coordinated effort – by government agencies, drug companies, health care providers, and patients themselves – can slow it down. As a starting point, however, one panelist suggested that the federal government develop a national baseline or report card on how the country is doing in diabetes – or better yet, a registry of some sort that at least tracks how many people have the disease. (The CDC's number – 21 million – is actually the estimated *minimum* number of diabetics in America and frankly no one really knows the number because there *is* no registry. Estimates for type 1 in the US range from 1 – 3 million.) Whatever the number of patients, Malcolm Gladwell said that the diabetes community needs to be part of a broader coalition (presumably with other chronic diseases) to effect health care reform. "You can't do a diabetes-only strategy," he said.

Panelists discussed at some length the need to replace what some have called "obesegenic communities" with healthier communities – nothing less, really, than redesigning neighborhoods where exercise and nutrition are prized, with better sidewalks and parks, improved physical education programs, healthier foods, safe streets, etc. Idealistic? Of course. But some major improvements *have* been made, such as the effort in Los Angeles to purge soda machines from schools[4]. Just as a journey of a thousand miles starts with a single step, broad systemic change starts with incremental improvement, and one of the encouraging themes from the Forum was the awareness that these reforms need to actually start *happening*.

Professor Martin Silink, new head of IDF, said that the new UN Resolution on diabetes demonstrates that the world has acknowledged the epidemic rates of the disease, and that there is a need for immediate action to slow the pandemic. Implicit is for all nations to raise public awareness and

[4] We remember a few years ago, for example, when it was said there was no *way* Dr. Francine Kaufman could change the state's position on soda in schools. And all anyone had to do was watch her. We continue to do here, hopefully, as she starts work with California Governor Arnold Schwarzenegger to garner healthcare coverage for all children in the state.

develop national policies on prevention, care, and treatment. The IDF, as part of its mission, will undertake systematic and regular global reviews of each nation's diabetes burden as well as the extent and success of its national care programs. The results of these reviews will be published annually on World Diabetes Day and at the IDF World Diabetes Congress. Encouragingly, Novo Nordisk also announced the launch of its Changing Diabetes Barometer, a comprehensive three-part study of societal attitudes toward diabetes, the economic state of diabetes and the state of clinical diabetes care in the U.S. This report card will provide benchmarks against which policymakers can measure improvements for diabetes. The first report is due to be published on November 1, in time for the first-ever UN-sanctioned World Diabetes Day, Nov 14, and it should give a sense of how countries are doing. We look forward to this important day in New York City.

Driving systemic change in the health care system was a clear theme among panelists. Any improvement in care has to involve changing the reimbursement system, which now rewards acute care, not chronic care. That means relatively little is reimbursed for education and disease management. But paying for those services won't be enough, argued Professor Elizabeth Teisberg, who co-authored with Michael E. Porter the book, "Redefining Health Care." As Teisberg told the audience, "The policy debates center on cost and payment shifting, but the critical actions are improving health and health care value." Specifically, she argues for a more market-oriented system that increases the value of care for the money spent – or what she describes as realigning competition around patient value. "Currently healthcare is structured around separate medical specialties, discrete treatments, and individual episodes of illness or injury." This is problematic because patients need coordinated treatment for their interrelated health conditions (such as a diabetes with hypertension or vascular disease), and they need it over the life of their disease – which, in the case of chronic conditions, means over the life of the patient. She also advocated pay-for-performance to motivate healthcare providers; to critics of pay-for-performance, she said that such a system would certainly be risk-adjusted to take into account the difficulty of the patients any given doctor accepts. I was reminded of a theme from James Hirsch's *Cheating Destiny: Living with Diabetes, America's Biggest Epidemic*: "…pay-for-performance is a bad idea whose time has come."

Dr. Francine Kaufman, the always-forward-looking head of the Center for Diabetes, Endocrinology, and Metabolism at Children's Hospital Los Angeles, laid out a series of suggestions for improving care for children:

- Guarantee access to high-quality comprehensive diabetes medical services that include routine diabetes management tailored to the specific needs and abilities of the patient and family, psychological support, and adequate quantities of diabetes supplies and medicines.
- Create schools in which all children have the ability to monitor their diabetes and receive timely and effective treatments, schools in which the food is healthy and the students are physically active and knowledgeable about what it takes to be healthy.
- Create communities that provide access to affordable fresh fruits and vegetables and safe places for children and families to be active.

These are clearly ambitious goals, but no change – large or small – is possible without global leadership, and that will only occur in response to public pressure. There was widespread agreement among the attendees that Clinton's statement about missing the severity of the diabetes epidemic was very powerful, particularly from a president who attempts to know as much as possible about everything. The more informed people can become – people with and without diabetes – the more likely they will advocate for the cause. Bill Clinton starkly presented the challenge in his final words to the audience: "Wherever you are from, shock people out of denial. Most people have no idea of the dimensions of this problem. We will never be forgiven if we allow kids to live shorter lives than they deserve."

—by Kelly L. Close

3. Novo Nordisk's Leadership in Diabetes

The Global Changing Diabetes Leadership Forum reflected, in our view, Novo Nordisk's global leadership. Diabetes doesn't have the awareness, both in the US and globally, that other diseases have, but the Forum's success raises the hope that the tide is turning. Certainly, the quick passage of the UN Resolution on Diabetes is further evidence that the international community is beginning to take heed. Diabetes is now one of only two diseases (AIDS is the other) that has its own UN resolution.

While the IDF led the lobbying efforts for the resolution, Novo Nordisk was also a big supporter. The resolution "is a platform for change," said Andrew Purcell, Novo's VP of Strategic Business Development.

Novo Nordisk has clearly worked hard to become a strong advocate for improving diabetes awareness, for educating patients, and for collaborating with other organizations to help physicians. For example, Novo is in the third year of a key initiative with the American College of Physicians to close the gap between current practice and acceptable standards of diabetes care, and to develop models for effective team-based care. Novo also continues to strengthen tools designed for patients, though the company is already at the top of the field on this one, in our view. For example, in late March, it revamped its www.changingdiabetes-us.com site, adding more patient-friendly guidance and more robust tools, such as personalized profiles and goal-setting programs. Such tools are terrific because they can help patients become more active in their own care.

Novo Nordisk demonstrates how a pharmaceutical company can drive change. Its National Changing Diabetes Program is a unique initiative in the US – and one that clearly requires a big investment. Novo says it's motivated by its business philosophy of "triple bottom line" – that the return at Novo must be measured on three aspects: financial viability, environmental responsibility, and social responsibility. The company says it makes a commitment to deliver the ideal outcomes for patients, and we're persuaded that's true. During our wide-ranging talk with CEO Sorensen, we asked him what concerns keep him up at night, and he immediately spoke of wanting to ensure the quality of Novo's products.

The goal of Novo Nordisk's National Changing Diabetes Program is to drive positive change for patients through collaboration. By convening key stakeholders in the diabetes community, particularly the medical associations – ADA, AACE, AADE, AAFP, ACP – and brokering consensus on messaging and policy priorities, NCDP wants to refocus our healthcare system from acute care to chronic care. This, according to Purcell, will drive better outcomes for patients. Purcell pointed to Dr. Teisberg's talk, which emphasized the need for measurement and transparency. On that front, Novo is taking a major step with its barometer program as well as through its examination of the impact of federal spending – trying to uncover where the federal government is spending money on treatment and prevention, and whether those contributions are actually making a difference. Novo has said it will work with the medical associations to give a consensus opinion in the next year.

Novo Nordisk is also deepening its focus on reimbursement. Payment structures in the US typically don't address behavior change and lifestyle counseling (with the possible exception of some managed care plans like Kaiser for type 2 patients), but Novo believes its models for patient education (e.g., the new website, which focuses on addressing psychosocial barriers to diabetes self-care) and its pipeline of newer drugs that are easier to take will help patients "connect the dots" to improve outcomes. We certainly agree that the simplicity of the newest drugs like Amylin's Byetta and Merck's Januvia will improve compliance and, as long as safety doesn't become an issue, improve outcomes. Novo's simpler-than-insulin incretin drug liraglutide, although several years behind Amylin's Byetta, is likely the next GLP-1 drug to be approved, probably in 2009/2010.

Says Purcell, "We really do want to defeat diabetes. The total company mission is to put ourselves out of business." However far-fetched it sounds, Novo is putting its money where its mouth is; besides all the professional and patient programs, there is heavy-duty research ongoing at the Hagedorn Research Institute in Denmark (www.hagedorn.dk/), an independent basic research component of Novo

Nordisk A/S devoted to finding a cure for diabetes and its complications. We had not heard of this institute before (more signs that with Novo, it's all about actions, not words), but were heartened to see on its website publications by scientists and students at the Institute dating back to 1978. Today, the site says, most scientists at Hagedorn (which includes a staff of 45) are focused on attempts to cure diabetes by reconstituting/preserving an adequate functional β-cell mass. Most of the research focuses on islet cell developmental biology, receptor biology and the pathogenesis of type 1 diabetes. It is envisioned that reconstitution of a functional β-cell mass with long-term immunological acceptance will re-establish euglycemia and thus prevent development of diabetic complications. JDRF and NIH also provide funding for the institute, and there seems to be a very strong commitment by Novo Nordisk toward addressing the biggest challenges in diabetes research.

—by James S. Hirsch and Kelly L. Close

4. Interview with Novo Nordisk CEO Lars Sorensen: on Bill Clinton, the company's new products, and more…

Lars Rebien Sorensen does not have diabetes, but he may be the most important business leader in the field today. As president and chief executive officer of Novo Nordisk, he heads the world's largest insulin company – its main product is used by 15 million people around the globe each day – and in our view, Novo is the most dynamic marketer in diabetes. What's more, Novo has taken the lead on raising awareness of the epidemic – most recently, by sponsoring the Global Changing Diabetes Leadership Forum in New York, which 155 leaders from government and health care and 30 journalists were invited to attend in mid-March, all of whom are affected by diabetes personally or professionally. To slow down the pandemic and provide adequate care for patients, three things are needed: vision, leadership, and money. Right now, Mr. Sorensen, and his company, is providing all three. Mr. Sorensen spoke to us from Novo's headquarters in Denmark. In a conversation with Kelly Close and Jim Hirsch, he talked about the need for governments to recognize that health care is not about treating diseases but about investing in the future, about Novo's future—its next generation of insulins and the opening of new markets—and about the need for the pharmaceutical industry to repair its reputation.

Kelly: Thank you so much for taking the time to speak with us. I found the Global Forum inspiring; so, taking the lead from that, we'd like to jump right in with some questions for you. One of the Global Forum themes really was that the scope of the diabetes pandemic has not been fully recognized by world leaders. We appreciated President Clinton's candor that his awareness wasn't as high as it should have been. Why do you think recognition among world leaders has been slow?

Mr. Sorensen: Well, now, I've worked for the company for 25 years, and for the last 12, 13 years in the health care business, and the first thing I did when I got involved in the health care business was to try to understand what was this company's approach and what was the customer community that we were serving. So I traveled the world and talked to patients. I spoke to patient associations and health care professionals to try to understand. So very quickly I became aware of the fact that diabetes was an unrecognized disease. There are two types of diabetes. Juvenile diabetes is attracting some attention and some support, and in fact the JDRF is doing a great job in trying to rally support for juvenile diabetes, whereas type 2 diabetes has been seen as an elderly disease – not a lot of sexy things from a medical perspective. And so there's been a lack of vocal advocates on behalf of people with type 2 diabetes to bring it further up on the political agenda. And so to me it was not surprising it was left, for many years, unattended. But now it's reached such an epidemic proportion that we know this is something we need to have recognized. And if we don't … hell will be upon us.

Kelly: Could you talk about what steps specifically you'd like to see industry, government, and health care professionals take to improve diabetes care?

Mr. Sorensen: I think we're basically talking about a problem of chronic disease, which is the biggest public health threat we have in many societies, in developed as well as the developing countries – 50 percent of mortality is due to chronic disease. And we believe diabetes is a model that can be used for how to deal with it, how to monitor it, how to treat it. But no single institution is able to solve this problem on its own, and therefore, we need to come together, the patient associations, the health professionals, governments, NGOs, and industry because otherwise we can't solve this.

Jim: But once everyone comes together, what should they be doing?

Mr. Sorensen: Well, I think we need to recognize that we each can play a role, and if we work together, I think there's a win/win situation possible. For example, ideally, we should create health care systems that are capable of preventing chronic disease, but if that's not possible, health care systems should diagnose and treat early rather than treating late. Then it's a win/win situation for everybody because diabetes is not costly if diagnosed and treated early, but it's very, very costly if it's left untreated. So there's an industry interest, looking upon it from our perspective. More awareness will lead to more diagnoses, which will lead to more advanced and more aggressive therapies, which leads to more business for the pharmaceutical industry. [Early diagnoses and treatment] would also help patients with less suffering and fewer complications. It would help society with reduced health care costs in the long run. So I think there is legitimate interest on behalf of all stakeholders in working together.

Kelly: How has the global diabetes epidemic affected Novo Nordisk – its product line, its R&D, or its mission?

Mr. Sorensen: I think when we look at the progression of diabetes, ideally we would like to cure diabetes, because that's what our customers, the people with diabetes, would really want. And since I cannot legitimately say it cannot be done, of course we should, as a pharmaceutical company, work at eradicating the disease, even though it would have some serious implications on our business. There are these scientific signs that it might indeed be possible. So it will be done at some point in time, and it might as well be us. But the time perspective on eradicating the disease is quite long. In the meantime, we need to look at the progression of the disease, and when we look at that, unfortunately we can see that there's still a higher risk for people with diabetes to develop complications and comorbidities associated with the disease. Therapies today are not sufficient for people with diabetes to live normal lives. And therefore there are still new drugs, and Levemir and GLP-1 therapy in particular are ways of addressing this. There are a lot of therapies that are being promoted today – DPP-4 inhibitors from Merck and Novartis in the future, as well. These are all new therapies, including inhaled insulins, which are more important for treatment of diabetes, more convenient for the patient. So there is a lot more that we can do from the research side as well. And then there is still a lot that can be done in terms of developing clinical practice guidelines and dietary guidelines so our people can appropriately treat themselves. There's an amazing lot of work that can still be done.

Kelly: It's fair to say that your biggest product, insulin, is under prescribed or under used, certainly in the US, because there're so many people who are taking it who are not at target. I wonder if you could just talk little bit about what you think Novo Nordisk or the other insulin companies should do to increase the use of the product?

Mr. Sorensen: It is interesting that diabetes and severe diabetes have often been associated with insulin therapy, so physicians would often encourage patients to treat themselves properly, to care for the disease, otherwise they would be put on insulin. So historically insulin was used as a threat in some ways, and to many patients, it was viewed as the end stage of the disease. Insulin had a bad connotation. For many years, it was also a belief that it increased cardiovascular risk. And all of these issues have been eradicated recently with clinical studies. It's increasingly being understood

that diabetes needs to be treated as aggressively and as early as possible, to reach near normal glycemic levels.

That is where the new therapies, like GLP-1, are important, because obviously when individuals are going from diet to oral therapy, oral therapies need to be improved, because patients are concerned about going directly to insulin. Insulin has traditionally had the side effects that you'd gain weight and that there may be hypoglycemia. The latter is not very significant as it relates to type 2 diabetes - it's more significant for type 1 diabetes. So GLP-1 has presented itself recently as an intermediate step between oral therapy and [insulin]. So we expect these new therapies will all find their own niche, and it's up to the physician and the patients themselves to decide how aggressively do they want to treat themselves, because we have to understand that the more aggressively the patients treat themselves, the more they infringe on their personal and private life in terms of either having to monitor blood sugar or having to take injections or multiple injections. And so it is a balance between the patient wanting to have a quality of life and the risk of developing complications long term.

Kelly: What has to happen, in your view, to make diabetes the urgent issue that you and I know it should be?

Mr. Sorensen: Well, I think you're touching on a very central thing, which is also one thing that I asked President Clinton about. It's going to be interesting to see how we will make significant change unless we also look at the financing of the health care system. In my country, where we have a public health system, we view prevention and early intervention as being investments – long-term investments in the future wellbeing of the population. Whereas in insurance-based systems, it's often difficult to see how they are able to invest, because people keep moving to different companies. And therefore the interest in investing in long-term prevention and health is significantly less. So in the US context, I think the main thing we need is to get major employers involved. We need to get the government involved because the government at the end will have the responsibility when uninsured individuals develop the complications of diabetes. And large employers will often carry the responsibility of their workforces for an extended period of time.

Jim: I assume what we need is a leader who can make that case - it's not just going to happen by natural evolution. Someone has to convince the employers.

Mr. Sorensen: That's true, but it was not only Bill Clinton who was at the Forum. It was also Newt Gingrich from the Republican side. We had worked with Newt Gingrich as we tried to engage the Clinton Foundation. And I think both of these leaders understand this issue. There has been, at least from our perspective, a revelation going on, where these political leaders can start to see that these chronic diseases, obesity in society, will become a huge burden unless we do something. And what we have to do is make a very long-term investment. It starts with education in schools, redesign of our cities – the whole redesign of our way of life.

Kelly: Maybe you could talk a little bit about your mission to defeat diabetes and what that means to you and what you think it means to your employees.

Mr. Sorenson: Well, it comes from a simple recognition, and that is if we align ourselves with the interests of people with diabetes, they're not necessarily thoroughly interested in our [business], they're interested in getting rid of that disease. So if I could just brush aside that wish that it was not technically, scientifically feasible, then we could go on selling our products. But I can't do that. I mean, we know there is scientific progress that seems to indicate there might be something we can do – stem cells and other therapies. And therefore we also have to engage in this and do our part, and as I tell my employees, it's better that *we* eradicate diabetes than somebody else. …We can be proud of it. And we'll find another business as part of the process. And if nothing else, we just made the final commitment to the disease. So if it can be done, it will be done.

Kelly: In light of that, what keeps you up at night? What do you worry about the most in terms of your business?

Mr. Sorensen: Well, I just spoke to a lot of our employees today [about this]. And one of the things I worry the most about is the quality of our products. We service about 15 million people with their daily needs of insulin, and if we don't make the proper quality and have the proper controls of our product, somebody is going to get hurt, and that's the worst thing … that could happen. We know there are risks involved in drug research, and that's a publicly understood risk. It's a risk that people that enter into these clinical trials understand, and they commit to that risk because they want to further research. So there are problems, of course. We try to avoid it but that's an inevitable risk we run. But not being able to supply adequate quantities of a high-quality product … could affect millions of people's lives. That's the worse fear I have.

Kelly: There was a *Wall Street Journal* article this morning about the risks associated with rimonabant – psychiatric risks and things like that – I wondered what you thought about Sanofi's strategy with this drug?

Mr. Sorensen: Well, I prefer not to comment specifically on Sanofi's approach other than to say that we are also interested in obesity, but we are interested in obesity from what we call the severe end. I don't believe that obesity prevention and treatment is a medical problem, in general. It's a social and cultural and societal problem that we need to deal with from a different perspective. But when we then see that there are groups of individuals, having had unsuccessful attempts to diet or exercise or at counseling, then we start to talk about medical intervention. And in that case, I think that perhaps GLP-1s might play a significant role in the future because we know the GLP-1 product actually reduces weight. But treating [people who are just slightly overweight] is absolutely not something that we want to do. Because these are, in many cases, healthy individuals that are just simply overweight to the point where it's not healthy for them in the long run.

Kelly: Right. And I guess as the Global Leadership Forum really showed, there are obviously so many other groups that need help more than that group of slightly overweight. You know, we wondered if you could just talk briefly about your impressions following the forum. Who were the biggest surprises and what were some of the biggest and most surprising take-aways?

Mr. Sorensen: I must say I've been to many international meetings, and I went to this one with some apprehension – I wondered if it was just going to be another meeting. But I think it has some historical implications. Other representatives from Russia, from India, different parts of the world were there, and so I think we will try to take this movement further and see if we can build on the interest that was created. We're certainly going to take and have already taken Mr. Clinton up on his word of potential collaboration, and we've already approached the Clinton Foundation. And we're going to be following up on this immediately.

Kelly: And I guess that's part of your work on the UN resolution?

Mr. Sorensen: Yeah, this whole thing is part of that because the UN resolution is nice but it does not really mean anything unless we put some concrete actions in place. This gives us, what would you call it, a right to bring up the agenda with different governments around the world, a right to demand on behalf of people with diabetes that national plans are being made, that targets are being made, and that we can follow up and help patient associations in setting that agenda. But unless we try to drive that, nothing is going to happen. There are many, many plans for eradicating poverty or eradicating health problems, and they've never come to anything. What's so interesting in this regard is I think here we have industry, we have NGOs, we have governments working together, and I think we can make a difference.

Jim: Are you optimistic that others in industry will help you?

Mr. Sorensen: Well, there's certainly room for it, to have other parties involved. We created an international foundation for diabetes, WDF [World Diabetes Foundation], independently. And we're now running 100 projects in different developing countries, and we donated $100 million to improving diabetes care. And for every dollar we put in, we had $3 matching funding coming from other sources, so we were actually reaching way further than our own resources. And I think what that initiative will lead to is other groups – our competitors – doing the same thing. And so we get into a positive spiral, rather than getting into this negative spiral of industry groups taking initiatives with little impact because there's no differentiation and there's no branding value in any of the activities. What we have done is force other players in the diabetes field to take complementary activities, and it will benefit the diabetes community globally.

Jim: The real time bomb in diabetes is in the large developing countries like China, India, the Pacific Islands, Southeast Asia – how receptive are those countries to insulin and how much success have you had in selling your product there?

Mr. Sorensen: Very much so. It is really rewarding to come to the developing countries, because people really receive all the knowledge and all the education and all the programs that we can help them with. And of course insulinization and therapies in these countries are much less advanced than what they are in the United States and in Europe. The diagnoses rates are much, much less. People are presenting with severe complications. But it is improving. We have entered into a collaboration with the Chinese government where as part of the company's initiatives and the World Diabetes Foundation that I talked about before, we're educating 50,000 Chinese doctors in building awareness around diabetes. This is unheard of in the Western countries. People would cry, oh, foul play, how can you interact with a single industry player? They need, and they'll take, all the help they can get. Which is quite interesting, and of course very rewarding for us as a company.

Kelly: It sounds like maybe we could learn something from that in the US.

Mr. Sorensen: But it does require that the industry lives up to that obligation of having integrity and being honest and responsible. And that's where, of course, our background in some cases has been a little bit shady. And we need to regain that ground as an industry.

Jim: How has that ground been lost?

Mr. Sorensen: I think it's been lost in some cases – largely unjust, but if you talk to the general public, the pharmaceutical industry is being viewed as self-serving and profiteering and profit-focused. But if you talk to the people that are affiliated with a specific disease and are dependent on scientific progress, I think their view is slightly more nuanced, as you probably are aware. There, people have perhaps a different feeling for pharmaceutical companies and the medical profession in general. But in the general public, unfortunately, we are not held in very high standing. Unfortunately. But it's to a large extent our own doing. And I'm not saying Novo Nordisk, but the industry in general, and that's just something we need to recognize. So we have to work a little harder.

Jim: Switching gears - regarding your products, can the insulins get better than where we are now, or is it now just a matter of finding smarter ways of dosing?

Mr. Sorensen: That is the most exciting thing, that right now we are working on developing yet another generation of insulins, which are, in our view, and perhaps in your own view, better than the traditional human insulins that we have used for many years. So Levemir, when you look at it, is a fantastic basal insulin, but it is still having a duration of action that is slightly less than 24 hours. It has the benefit that you're not gaining as much weight as the traditional NPH or long-acting insulin. When we look at our research portfolio, we have in early research and early clinical trials new and further improved basal insulins. And these basal insulins might even be formulated as premixes, so two-thirds of the whole market, the basal insulins in the premix, we believe that we might even be able to improve further than where we are today. We're still talking about something which may not

be available until another five years, but it's very, very encouraging research that we're seeing at the moment.

Kelly: This would be even beyond the analogs, like a super analog or something like that?

Mr. Sorensen: Yes. We prefer to call them modern insulins. So you have animal insulin, human insulin, and then you have modern insulin, and you can call the others postmodern insulins. But it's yet another generation, which has some further properties. Whether we can improve it even further from that, I don't know at this point, but this will give significant benefit to those that use our products. I'm quite certain about that.

Kelly: Do you have any comment on inhaled insulin and what you think the prospects are?

Mr. Sorensen: Well, inhaled insulins are something we're working on as well. So far the concepts that have been presented are not really offering any clinical benefit. They are rather offering convenience for those that want to make a transition from oral therapy to insulins. And that, in itself, for some individuals represents a major hurdle and therefore should not be underestimated. But the current prototypes, if I may call the product that we have in development and that Pfizer has in promotion, are not going to be the long-term product for pulmonary administration. We shall see whether we are able to – and Pfizer and others – are able to modernize these even further. And compared to any technological development, mobile phones or CD players or what have you, obviously they will improve and become more convenient. The question is then whether they will also be able to offer long-acting insulins in pulmonary form and therefore make a more complete portfolio of products with that administration. We might even be able to offer oral insulins, but that is still some ways out into the future. But that would of course be highly interesting for everybody if we could develop an oral insulin.

Kelly: Thank you so much for speaking with us and for providing so much leadership in the field.

—by James S. Hirsch and Kelly L. Close

5. Conference Report

- **2007 AMS Scientific Meeting on Diabetes and the Gut, March 1-4, Grand Bahamas Island**

Below we present our conference highlights from the 2007 American Motility Society Scientific Meeting – "Diabetes and the Gut" – which took place from March 1 to 4 at Our Lucaya Resort in the Bahamas. At the opening session, we learned that the AMS (which is a gastroenterology association) was focusing on this topic because of the recent NIH crunch on research funding. It is said that the leaders of the society got together last year and decided the best way to secure scarce research funding for their field would be to focus their research on more specific topics. They decided that diabetes would be best – hence, their theme for 2007 – and they invited a number of speakers whose research may not be on GI but who have done work in diabetes. We thought this was a fascinating back-story, and a powerful reminder of how important diabetes has become in the medical and research community.

Dr. Bo Ahren of Lund University gave the only talk on incretins at this meeting, with one exception (a short abstract presentation showed that vildagliptin – Novartis's Galvus – appears not to slow gastric emptying or glucose entry into the bloodstream; more evidence, we think, that DPP-4 inhibitors are not as powerful as GLP-1 at controlling postprandial glucose). Dr. Ahren spent some time giving background on incretins before discussing the therapies available now. Notably, he believes that glucagon suppression is the biggest contributor to the effects of GLP-1 on hyperglycemia. He also believes that GLP-1 preserves b-cells. He presented data on both exenatide (Amylin's Byetta) and liraglutide (Novo Nordisk) and seemed certain the latter would be approved "soon." He also seemed to assume that Galvus would be available in the future, in spite of the recent regulatory setback (approvable letter). He believes the most important differences between incretin

mimetics and DPP-4 inhibitors are the injected administration of the former and the lack of effect on gastric emptying and weight from the latter.

Dr. Steven Shoelson of Harvard addressed his work in the seemingly super-hot area of inflammation and diabetes. He reviewed the idea that NF-kB activation is responsible for mediating the effects of obesity on inflammation, insulin resistance, and cardiovascular disease. He is currently conducting the TINSAL-T2D phase 2/3 trial to test high-dose salsalate (an inhibitor of NF-kB) for type 2 diabetes, as well as planning a large 900-person trial to test whether salsalate can reduce or prevent soft non-calcified atherosclerotic plaques in patients with a history of coronary heart disease and metabolic syndrome.

Neuropeptides came up in several talks – notably, Dr. Anthony Ferrante of Columbia University gave a talk on the discovery of leptin. While leptin has not succeeded as a therapeutic for obesity to date, at least in monotherapy, he noted that it has helped researchers discover many other neuropeptides. He also talked about his research on inflammation in diabetes and a receptor called CCR2 that seems to contribute to monocyte infiltration into adipose tissue – one of the physiological abnormalities believed to contribute to insulin resistance. This was very interesting. We also enjoyed listening to Dr. Giamila Fantuzzi of the University of Illinois at Chicago talk about the inflammatory roles of leptin, ghrelin, and adiponectin in intestinal inflammation – in diabetes we usually think only about the metabolic effects of these hormones, but they actually play other roles in physiology as well, including inflammation and cellular proliferation.

Diabetic gastrointestinal motility was a big theme of this conference. One of the most interesting things we learned about was the high prevalence of gastroparesis (delayed gastric emptying) among patients with diabetes. Estimates suggest that at least a third of patients with longstanding diabetes have gastroparesis, yet the condition is not usually diagnosed because the GI symptoms that would normally prompt doctors to check for the condition are actually not well correlated with the speed of gastric emptying – i.e. many patients with gastroparesis are asymptomatic and some patients complain of abdominal problems despite having normal gastric emptying. The relevance of this to diabetes therapy is that the speed of gastric emptying affects therapy – delayed gastric emptying is always a good thing in non-insulin-treated type 2 patients, but for patients on insulin it can actually make it harder to time insulin administration (shots or boluses) if they are not aware of the problem.

Neuropathy was also a big theme of many talks. Treating neuropathy remains very challenging. Dr. Philip Low of Mayo Clinic spoke about targeting oxidative stress to treat diabetic neuropathy using a-linoic acid, a strong anti-oxidant. Several German neuropathy trials have suggested that there is a benefit with a-linoic acid. Dr. Low said that a trial like the DCCT, which looked at a very early point in the prevention of neuropathy, would be the best setting to test a-linoic acid therapy. Of course, there are so many reasons why another DCCT could not be put together, most of them related to resources, but we found this talk to be interesting because it reminded us that it's not just treatment of diabetes itself that needs to be earlier and more aggressive, but also treatment of diabetic complications like neuropathy.

Type 1 diabetes – still working on the cure. Dr. Massimo Trucco of Children's Hospital in Pittsburgh gave a fascinating talk on his work with trying to cure type 1 diabetes. In type 1 diabetes, auto-immune T cells of the immune system attack and destroy b-cells. Dr. Trucco believes that if those auto-reactive T cells can be eliminated, there is still a possibility of regeneration even if all the b-cells in the pancreas are gone. This has been shown in non-obese diabetic (NOD) mouse models. After two to three months, there are new islets that are not actually islets, but more like an agglomeration of insulin-producing cells. In his talk Dr. Trucco discussed an NIH-funded phase 1 safety trial that he is currently conducting to test a technique to engineer dendritic cells to down-regulate the auto-immune T cells responsible for b-cell destruction. We thought this trial was quite

interesting and will want to see how well the method works if he gets the chance to study it further in future efficacy studies.

—by Jenny J. Jin

6. PTP1B Inhibitors: More Help on Insulin Resistance*

Why We Need Insulin Sensitizers

The two main types of diabetes have gone by different names over the decades (remember the confusion caused by 'juvenile-onset diabetes' and 'non-insulin dependent diabetes'?), but the current 'type 1' and 'type 2' terminology has served well for some years now. One thing we like about this classification is that it serves as a convenient reminder that while type 1 diabetes is characterized by one major defect – loss of the b-cells – type 2 diabetes is characterized by *two*: insulin resistance and b-cell failure. While there is some debate about which comes first and which is more important, we would submit that it almost doesn't matter, because regardless of which is the chicken and which is the egg, both defects need to be treated.

The rise of the incretin and amylin drug classes in recent years has gone a long way in addressing the b-cell part of the problem. Right now it's still anyone's guess whether these drugs produce a lasting benefit on b-cell mass, but in clinical trials so far they have shown good durability of efficacy (out to three years of open-label data for exenatide) and a real effect on increasing β-cell secretory function. But while incretins sometimes seem like wonder drugs, they don't do everything. In particular, no matter how good of a job they may do on β-cells, they do not address the problem of insulin resistance in type 2 diabetes. Certainly, the significant weight loss seen in some patients who take Byetta or Symlin should cause a secondary lowering of insulin resistance, but many patients – about 20% – do not lose weight on these drugs. As a result, in some patients an insulin sensitizer may make sense.

Of the two major insulin sensitizer classes available, metformin works well on hepatic insulin resistance but not on other tissues (muscle, fat, etc.), whereas the thiazolidinediones (TZDs) are limited by significant side effects of weight gain, edema, association with congestive heart failure, and of late, fractures, at least in women. This is unfortunate because in many other respects they're great drugs – they target insulin resistance throughout the body, show some improvement of numerous metabolic risk factors, and are currently the only treatment proven equal to lifestyle modification when it comes to diabetes prevention. We don't know if an insulin sensitizer that works through a different mechanism than PPAR-γ agonism would produce all of the same benefits as the TZDs, but one potential new mechanism that intrigues us is PTP1B inhibition.

Leptin Resistance Accompanies Obesity

One interesting defect that accompanies insulin resistance in obese patients is leptin resistance. Circulating levels of both insulin and leptin are elevated in obese individuals. The hormone leptin acts as a measure of the body's energy stores: when someone loses more than 10% of their body weight, their leptin levels will drop below a critical threshold and trigger the body's 'starvation response.' Metabolism slows, energy expenditure drops, and appetite increases in order to promote weight regain.

In leptin resistance, the body stops responding to even very high circulating levels of leptin, and the 'starvation response' is permanently turned on. Some of the few known monogenic (single gene)

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mutations that can cause obesity in humans are defects in either the leptin gene (like ob/ob mice) or the leptin receptor gene (like db/db mice). Most obese individuals aren't missing either leptin or the leptin receptor, however; they're simply leptin resistant. (See DCU #61 for our article on Dr. Robert Lustig's theory about how modern diets may be causing insulin resistance, leptin resistance, and childhood obesity.) Leptin resistance is why simply giving leptin to an obese individual typically has only a small effect. Theoretically, however, administering a leptin sensitizer might be able to produce anorectic effects that leptin itself wouldn't be able to produce.

The Molecular Biology: Insulin Receptors, Leptin Receptors, and PTP1B

The fascinating thing about protein tyrosine phosphatase 1B (PTP1B) is that it inhibits both insulin receptor and leptin receptor signaling, which means that inhibiting PTP1B in turn should restore both insulin and leptin receptor sensitivity and treat both type 2 diabetes and obesity. Here's for a quick review of the molecular biology of insulin and leptin receptors: *(readers – please skip the next three paragraphs if not interested in the nitty-gritty biology details)*

The insulin receptor belongs to a class of membrane receptors called receptor tyrosine kinases. In biology, kinases are defined as enzymes that attach phosphate groups to their target proteins. This action (called phosphorylation) usually activates the target protein. The insulin receptor is normally inactive, but when insulin binds to it, it becomes an active kinase and phosphorylates its target proteins: IRS1, IRS2, IRS3, and IRS4 (insulin receptor substrates). Once phosphorylated and activated, these IRS proteins trigger further downstream steps in the insulin signaling pathway that eventually stimulate the cell to take up glucose from the bloodstream and to synthesize glycogen, fatty acids, and proteins.

PTP1B inhibits the insulin signaling pathway by cutting it off right at the beginning. In biology, phosphatases are defined as enzymes that remove phosphate groups from their target proteins in a process called dephosphorylation. PTP1B removes phosphates from the IRS proteins, undoing the insulin receptor's work. Even worse, one of the important features of the insulin receptor is that it actually needs to phosphorylate itself in order to fully activate its own tyrosine kinase activity. PTP1B also dephosphorylates the insulin receptor, further inhibiting activation of the insulin signaling pathway.

Interestingly, the leptin receptor is also a receptor tyrosine kinase, though its downstream target is the JAK2/STAT3 signaling pathway. When leptin binds to the leptin receptor, the receptor's tyrosine kinase activity becomes activated and it phosphorylates JAK2, which in turn activates the rest of the JAK2/STAT3 pathway. PTP1B also dephosphorylates JAK2, thus inhibiting activation of the leptin receptor signaling pathway.

The upshot of all of this is that inhibition of PTP1B would prevent inhibitory dephosphorylation of key proteins in the insulin and leptin signaling pathways and would thus stimulate insulin and leptin receptor signaling in cells throughout the body (muscle, fat, liver, etc.). This would sensitize these peripheral tissues to normal circulating levels of the hormones insulin and leptin and possibly overcome the pathological insulin and leptin resistance observed in type 2 diabetes and obesity.

The Pipeline: PTP1B Inhibitors for Type 2 Diabetes

PTP1B activity seems to be elevated in people with obesity and type 2 diabetes. People with genetic mutations that cause overexpression of PTP1B tend to have insulin resistance as well as high triglycerides and HDL. Conversely, PTPT1B knockout mice are insulin sensitive and resistant to weight gain when fed on high-fat diets; also, they don't seem to suffer any particular abnormalities, which is promising in terms of the safety of PTP1B inhibition. All of this suggests that PTP1B would be a good target for treating type 2 diabetes and obesity.

Several companies have been working for years to develop small molecule inhibitors of PTP1B for type 2 diabetes, but the problem has proved surprisingly difficult. This is because PTP1B's active site likes to bind to molecules with negative charges, which means that a good competitive inhibitor of PTP1B would

have to be negatively charged. Unfortunately, in order to get past cellular membranes and into cells, small molecule drugs generally need to be hydrophobic (neutrally charged and nonpolar).

RNA interference using antisense oligomeric inhibitors of PTP1B expression is one alternate approach to small-molecule drug discovery. This approach takes advantage of the fact that double-stranded RNA molecules are quickly destroyed in human cells. The idea is to synthesize nucleic acid strands (oligomers) that are complementary to PTP1B mRNA and then inject them into patients. These oligomers will hybridize with the mRNA that codes for PTP1B and the resulting double-stranded RNA will be promptly destroyed. Without any mRNA to direct PTP1B protein synthesis, levels of PTP1B in the cell will fall. ISIS Pharmaceuticals has an antisense drug (ISIS 113715) in phase 2 development for type 2 diabetes. This has been characterized as the lead PTP1B inhibitor in development but that is difficult to say.

There are many other companies working on drug candidates in the PTP1B arena. Wyeth previously had a small-molecule candidate in development but it was pulled from the pipeline after failing phase 2. Companies that we believe have PTP1B compounds currently in development (most pre-clinical or phase 1) include: Ceptyr/Lilly (CPT633), Array BioPharma/Amgen, Alinea, Metabasis, TransTech Pharma, and Akros Pharma/JT Pharmaceuticals.

Publications on PTP1B inhibitors in the literature include papers by scientists from Pfizer, Abbott, Roche, Merck, AstraZeneca, Novo Nordisk, Aventis, Genentech Inc., Cengent Therapeutics, Serono, InCyte, BioCore AB, Proctor & Gamble, Affymax Inc., Sunesis, Proteonik Inc., Pharmacia, Biovitrium AB, and Taisho.

—by Jenny J. Jin

7. In the News

- **CCMS - Competitive bidding for mail order diabetes supplies to begin**: The Centers for Medicare & Medicaid Services (CMS) announced April 2 that it would begin implementing a competitive bidding program for 10 categories of durable medical equipment (DME) and supplies in 10 of the largest metropolitan statistical areas (MSAs) in the country. About three million Medicare beneficiaries (of whom diabetes supply company PolyMedica estimates ~360,000 test blood glucose) will be included. The bidding process will begin in late April, with bids due in June. CMS will award contracts by late 2007. The competitive bid prices will go into effect in April of 2008. For the 12 months beginning April 2008, the competitive bid prices will replace the current Medicare fee schedule in the participating MSAs. In April 2009, competitive bidding will go into effect for the 80 biggest MSAs in the country – CMS has not yet announced which additional MSAs will fall under this umbrella. Once bid, winning suppliers' prices will be fixed for the three years of the bid contract, with no annual adjustments for inflation. Notably, only mail-order diabetic supplies other than meters will be affected. These include test strips, lancets, etc. but not blood glucose meters. CMS says that patients' choice of BGM will not be affected by the new policy because winning suppliers will be required to supply the same brands of test strips to Medicare beneficiaries as they do to non-Medicare patients. About 60% of all Medicare beneficiaries currently receive their diabetic supplies through mail order (vs. retail pharmacy), so this ruling will affect the majority of beneficiaries. Beneficiaries will still have the option of either getting their supplies through mail order or directly from pharmacies. Under the CMS rule, bidding suppliers must be accredited (or in the process of accreditation) by Medicare, meet certain (rather complex) financial standards and reporting requirements, and have a Medicare supplier number. To protect small businesses, there will be a 20% participation target for small suppliers whose gross revenues are $3.5 million or less, and small suppliers will be allowed to network together to pool purchasing power, though the short bidding timeline may make this difficult. CMS has stated that it will not apply the "inherent reasonableness standard" without further rulemaking and comment (i.e. it will not use data collected from the competitive bidding process to set reimbursement rates for non-competitively bid areas). Said Robert

J. Knorr, Senior Advisor to COGENT Reimbursement Strategies, Inc.[5], "Excluding only glucose meters for mail-order suppliers is a hollow victory for blood glucose manufacturers who derive a small portion of revenue from heavily discounted meters. Ultimately, mail-order suppliers are the big winners. Award-winning suppliers will continue to exert significant influence on patient choice and billable strip utilization. At the same time their negotiating position with strip manufacturers will continue to increase under the current Competitive Bidding model. The irony is that one of the objectives of Competitive Bidding was to reduce the cost of waste and abuse inherent in certain DME categories and diabetes testing supplies in particular. This has been an area of concern to CMS and the OIG for years. Ultimately, there are missed opportunities on two fronts; first for manufacturers to deliver improved value to CMS by changing their basic value proposition (i.e. from blood glucose measurement to true monitoring) and secondly for CMS to reward DME suppliers who offer products and related services which help CMS reduce real waste in the system." We strongly believe offering broad diabetes education and support are among the most critical pieces to help patients "connect the dots" between checking their numbers and knowing how to change their behavior. Educated behavior, of course, helps not only patients and their families but also manufacturers, since patients in the know who really understand the meaning of the numbers are also likely to test more frequently to get the data that will improve their health. In turn, this helps avoid short- and long-term complications, which – you *know* where this is going – helps the payors and the taxpayers.

- **A diabetes registry in New York City public hospitals and a PCP perspective:** In January, a letter to the editor in the New York Times from Alan Aviles, the president of the New York City Health and Hospitals Corporation (HHC), discussed an electronic registry that records glucose levels, cholesterol, and blood pressure for New Yorkers with diabetes; the registry has apparently improved A1cs. We spoke with some representatives from the HHC: Dr. Louis Capponi, an internist from New York University, and James Saunders of the HHC. The registry is now being used in all eleven public hospitals in New York City, for a population that is largely uninsured and suffers a high rate of diabetes. The registry collects data for diabetes health outcomes and is presented in a user-friendly way to care providers, mostly nurses and PCPs. Inspired by the results of an initiative in Queens last year, the HHC began using the registry in an initial cohort of 13,000, the percentage of whom had A1cs under 7% has now increased 18% from 35% to 42%. Now being used in about 50,000 people, the HHC hopes to double the amount of people who are well controlled by the end of 2008. The Queens Health Network, which has been doing something similar since 2002 and has apparently doubled its percentage of patients with A1cs under 7% (specifics were unavailable – it would be great to know the absolute number of people with A1cs under 7%). The near-20% change the HHC has seen, though, is still large, given that little improvement is seen in New York's public hospitals. Moreover, for this population, a cut-off of 7% does not reflect A1c improvements from, say, 10% to 8%, which is also meaningful. What's more, the registry is starting to include such information as whether a patient has a self- management plan, as well as results from eye exams, foot exams, depression screening, and so on. As a result, one could do complex analyses by population (e.g. determining the average A1c among people on insulin, etc.). The next step for the HHC is to get providers to actually start using the registry. Dr. Capponi was concerned that New York had a shortage of mental health professionals, since diabetes requires depression screening. He said HHC goes for generic drugs whenever possible, but it's pushing for more insulin use, including insulin analogs. There are heavy barriers to insulin use in this population. Insulin, of course, can be dangerous if used improperly, and many patients here are not literate in English or significantly knowledgeable about health issues.

[5] COGENT Reimbursement Strategies, Inc. has a plan called "Reimbursement Pathways[SM]" to maximize valuation for medical technologies. For reimbursement advisory, please call COGENT principal Andrea Bloom at 925.487.9370.

- **Body Volume Index – a more expensive, more accurate replacement for BMI?** At the American College of Cardiology meeting (highlights coming in next month's issue), we heard over and over that BMI was not an accurate measure of cardiometabolic health. Intra-abdominal adiposity, or visceral fat, has a much greater correlation with poor health outcomes than total fat. The BBC reported on March 23 on a new measure called the Body Volume Index or BVI. This measure takes into account how much fat a person carries as well as the person's body shape, which we know is important to cardiometabolic health (apple-shaped vs. pear-shaped). The problem is that calculating BVI, which requires more measurements than just the height and weight measurements of BMI, is much more expensive and requires a 3D scanner. That's a major downside – one of the best things about BMI is that it is both easy to use and inexpensive. A study, called the Body Benchmark Study, will scan 20,000 people over the next two years as part of clinical testing of the scanner, created by Select Research. It hopes BVI will replace BMI. We can't imagine that will be possible near-term (and possibly longer-term), although Select Research claims that scanners will be affordable for GPs. We'll have to see the payoff – but plenty of people insist on determining BVI in websites after hearing about it. See www.bodybenchmark.org - we do know we can't wait to try it!

—by Daniel A. Belkin, Jenny J. Jin, and Kelly L. Close

8. Reviewing the Diabetes Literature: Conservative recommendations for IFG/IGT

Below is our list of the 25 most important articles on diabetes and obesity published since our February DCU. We're always looking for the most relevant articles on new research, and we've compiled papers from journals including *Archives of Pediatric and Adolescent Medicine, Diabetes Care, JAMA, Nature Medicine, Lancet, International Journal of Obesity,* and more. This month we feature our lit review of a consensus statement on the treatment of IFG/IGT developed by Dr. David Nathan and a panel of colleagues and published in *Diabetes Care*.

- *Arch Ped Adol Med - Bariatric Surgery in Adolescents: Recent National Trends in Use and In-Hospital Outcome - Tsai et al*: The annual number of bariatric surgeries performed on adolescents remained constant from 1996 to 2000 but tripled from 2000 to 2003, with 771 procedures performed in 2003. This represents 0.7% of all bariatric surgeries performed in that year, so it's clearly a very low percentage, but growing quickly. In-hospital complication rates are similar between adolescents and adults, but the former tend to have shorter lengths of stay. No in-hospital deaths have been observed to date for adolescents (the mortality rate for adults is 0.2%).
- *Arch Ped Adol Med - Prevalence and Health Care Use of Overweight Children in an Integrated Health Care System - Estabrooks, Shetterly*: The authors examined data from 11,636 children in the Kaiser Permanente Colorado system from 2000 and 2004. They found that 13% were overweight and 15% were at risk for becoming overweight. Overweight children had more medical visits – 11% at year one and 6% at year three. Notably, they tended to use more mental health services. The percentages might sound low, but the authors estimate that the annual extra cost of use for 1,000 overweight children is $42,000 in primary care and $32,000 in mental health care. This seems cheap to us given that without this kind of primary care, ongoing medication or potentially surgery for even one obese child who develops type 2 diabetes will far outweigh these costs.
- *British Journal of Pharmacology - Effect of Rimonabant on Nociceptive Responses and Adjuvant-induced Arthritis in Rats - Croci, Zarini*: This paper highlights the anti-inflammatory and anti-hyperalgesic effects of rimonabant in obese animals, suggesting that it could provide a more general and aggressive strategy to protect obese patients from future risks. An accompanying editorial by Costa notes that obesity is considered a mild inflammatory condition, so maybe a successful way to treat obesity is a therapy combining weight-reducing drugs with anti-inflammatory ones... such as rimonabant. He notes that rimonabant's anti-obesity action is accompanied by favorable changes in markers for insulin resistance, CRP, adiponectin, and TNF-α. It certainly seems true to us that rimonabant lowers cardiometabolic risk factors (we can't believe we're using this phrase so blithely)

in some people; seeing the risk assessment tradeoffs in the FDA panel meeting on rimonabant scheduled for June 13 promises to be very interesting.

- [***]*Diabetes Care - Perceptions of Psychosocial Factors and the Insulin Pump - Ritholz et al:* Patients who think of their pump as a tool rather than a panacea for meeting their glycemic goals tend to have a more active approach to their diabetes management and better control. Not surprisingly, women are more concerned than men about body image and social acceptance with pump use. The authors conclude that active self-care, realistic expectations about the pump, and strong emotional memories of diabetes diagnosis are associated with better glycemic control and lower A1c in pump users.
- [***]*Diabetes Care - Classification of Distinct Baseline Insulin Infusion Patterns in Children and Adolescents With Type 1 Diabetes on CSII Therapy - Holterhus et al:* Pediatric endos use distinct basal insulin infusion rate profiles in CSII patients depending on age, possibly due to the circadian rhythm and endocrine changes of puberty. The authors looked at basal insulin infusion rates from 1,248 type 1 diabetic patients on CSII (aged 0.38-18 years). The profiles fit into two major groups: Group one showed a dawn-dusk pattern and included 708 patients (14.9 ± 2.4 years) who had peak basal insulin infusion rate at 5 am. Group two included younger children, who tended to have only one basal insulin infusion rate oscillation per 24 hours with the peak being slightly later in younger children than for older children (n = 152 for peak at 1 am, mean age 12.4 years; n = 117 for peak at 9 pm, mean age 8.9 years).
- [***]*Diabetes Care - Insulin Resistance, the Metabolic Syndrome, and Complication Risk in Type 1 Diabetes: "Double diabetes" in the DCCT - Kilpatrick et al:* Interestingly, metabolic syndrome is not associated with greater complications in intensively treated type 1 patients. In the DCCT, the intensively treated cohort had a higher incidence of metabolic syndrome in follow-up than the conventionally treated group – mostly associated with greater weight gain – but this was not associated with a higher risk of complications. Of the two measures of insulin resistance researchers examined, glucose disposal rate but not insulin dose was associated with the development of complications.
- [***]*Diabetes Care - Two-Year Safety and Efficacy of Inhaled Human Insulin (Exubera) in Adult Patients With Type 1 Diabetes - Skyler et al:* The important takeaway from this piece appears to be that THE pulmonary-function decline associated with Exubera therapy is not progressive. Declines in pulmonary function, as measured by forced expiratory volume and carbon monoxide diffusing capacity, are largely limited to the first three months after the therapy begins, and these measures of pulmonary function remain stable afterwards for up to two years. While glycemia was similar in both the inhaled and subcutaneous groups, hypo rates (2.8 vs. 4.1 events/100 subject-months) and weight gain (+0.8 kg vs. +2.0 kg) were somewhat lower with Exubera, which all else equal would certainly be positive for inhaled insulin.
- *Diabetes Care - Effect of Point-of-Care on Maintenance of Glycemic Control as Measured by A1C - Petersen et al:* In this study, implementation of point-of-care A1c measurements was associated with improvements in patients' mean A1c. Medical records from a year before POC was implemented and three years afterwards showed a steady decline in mean A1c compared to no improvement in A1c at a separate clinic where POC was not available. (POC means patients get their A1c taken and they receive the result right away so they can discuss with their doctor at the visit.) This suggests a benefit, and we strongly believe that having the A1c score at a patient's appointment with a healthcare provider can make a world of difference.
- *Diabetes Care - Simultaneous Control of Hyperglycemia and Oxidative Stress Normalizes Endothelial Function in Type 1 Diabetes - Ceriello et al:* Treatment of both hyperglycemia (with

[***] We thought this review was especially noteworthy. Space does not permit us to go into more details here, but if you would like our full-length review of this piece, please write litreviews@closeconcerns.com.

insulin) and oxidative stress (with vitamin C) are necessary to normalize endothelial dysfunction and reduce oxidative stress in type 1 patients. Neither treatment in isolation normalized endothelial dysfunction or reduced oxidative stress. This means that normalizing hyperglycemia is part of reducing oxidative stress, and that while it is necessary, it is not sufficient to normalize endothelial dysfunction. We note that this article by key thought leader Dr. Ceriello adds to the knowledge base regarding the link between glycemia and oxidative stress.

- *Diabetes Care - Insulin Secretion and Insulin Sensitivity in Relation to Fasting Glucose in Healthy Subjects - Ahren:* Even in non-diabetic women who are within the normal limits of glycemia, higher fasting glucose is associated with greater insulin secretion and less insulin sensitivity. Dr. Bo Ahren, noted specialist in incretins among other areas of research, showed that women in higher quartiles of fasting blood glucose had less insulin sensitivity as measured by euglycemic hyperinsulinemic clamp and greater insulin secretion as measured by a glucose-dependent arginine stimulation test.
- *Diabetes Care - The Impact of Glycemic Control on Neonatal Outcome in Singleton Pregnancies Complicated by Gestational Diabetes - Gonzalez-Quintero et al:* Neonatal complication rates are significantly higher in infants born to women with GDM with suboptimal blood glucose control, compared to those with optimal control. This is unsurprising. In their study, Gonzalez-Quintero and colleagues found that the likelihood of having at least one complication was 33.1% in infants born to women with suboptimal blood glucose control compared to 24.0% in infants born to women with optimal control. The big surprise to us from this study was actually that the difference wasn't higher. The rates for specific complications varied: macrosomia (15.7% vs. 9.3%), large-for-gestational-age (19.8% vs. 11.1%), hypoglycemia (9.3% vs. 7.1%), jaundice (10.1% vs. 8.4%), or stillbirth (0.3% vs. 0.1%).
- *Diabetes Care - Diabetic Retinopathy and Diabetic Neuropathy - Bloomgarden:* This is the sixth in a series of thought-provoking and insightful articles that Dr. Bloomgarden has written on presentations at the 2006 ADA. This one focuses on diabetic retinopathy, neuropathy, and lower extremity vascular disease. Many new therapies are in development for diabetic neuropathy, including octreotide, statins, fibrates, and several more molecules being tested in animals – far more than we realized. As Dr. Bloomgarden writes, there is evidence that retinopathy is a good proxy for macrovascular complications such as cardiovascular disease – this could ultimately teach us much about treatment for complications. Diabetic neuropathy is more complicated – several anticonvulsants are being tested, but in general, these treatments can be worse than the disease.
- *Diabetic Medicine - Initial Monotherapy With Metformin or Sulphonylureas Fails to Achieve or Maintain Glycemic Goals - Cook et al:* This study examined electronic records of 6,532 type 2 patients from 280 primary care centers in the UK. Patients with low baseline A1c and drug initiation within three months of diabetes diagnosis were more likely to reach glycemic goal. It seems obvious to us that low A1c makes it easier to reach goal, but the point about early drug initiation is a good argument for aggressive therapy. The authors write that depending on baseline A1c, 24% to 88% of patients initiated on SFUs achieved A1c <7% at one year after diagnosis, while 19% to 86% of patients on metformin did. We always have trouble with studies showing such big ranges – but in general, we believe more trials should be reported showing the impact of initial combo therapy for many type 2 patients – Janumet may be able to help the significant proportion of patients for whom monotherapy isn't doing the job, but we would look for more robust studies before writing home about it.
- *Diab, Obes, Metab: CSII Leads to Immediate, Stable and Long-term Changes in Metabolic Control - Aberle et al:* This study tracked 52 patients with type 1 diabetes for one year before and four years after they began using insulin pumps. In the first quarter after CSII was initiated, A1c dropped from 8.2% to 7.3%, and over the course of the next four years remained at a mean of 7.2%. The authors say this shows that CSII has both an immediate and stable long-term benefit on A1c. While we find the

data encouraging, we note there was no control group. Oddly, the authors report that the standard deviation of A1c variability *between* patients decreased from 3.02% to 1.23% with CSII onset but they did not study glycemic variability for individual patients, which we think was a significant omission because reducing glycemic excursions is a critical reason that patients go on pumps.

- *Diabetes/Metab Res & Rev - Insulin-based Regimens Decrease Mortality Rates in Critically Ill Patients - Langley, Adams:* According to this 16-study meta-analysis, the literature suggests maintaining normoglycemia with insulin-glucose-potassium (GIK) infusion, insulin-glucose infusion, or insulin therapy reduces the risk of organ damage in critically ill patients in the hospital, and seems to reduce mortality and morbidity. Nonetheless, not all the studies published to date are positive; some suggest either no benefit or even some harm. The general consensus at ACC seemed to be that GIK is actually not beneficial.
- ***Diabetes Tech & Thera - Adverse Impact of Temperature and Humidity on BGM Reliability - Haller et al:* This study tested eight BG meters and test strips in an environmental chamber for 50 days, subjecting them to a range of temperature (54-87°F) and humidity (49-100%). The meters tested included Bayer, LifeScan, Abbott, and Roche products. The authors found that all were unreliable at temperatures and humidity within the manufacturers' stated limits – for example, each 1°F increase in temperature caused a 1.13 mg/dL decline in accuracy for one meter. It is not clear if these problems were related to the test strips or the meters themselves; perhaps environmental conditions affect the enzyme chemistry used to measure glucose. The authors warn that this could impact patients' daily diabetes management.
- ***International Journal of Obesity - Cetilistat (ATL-962), a Novel Lipase Inhibitor - Kopelman et al:* The phase 2 trial of cetilistat (Alizyme's lipase inhibitor, which has the same mechanism as orlistat) suggests the drug has low efficacy but good tolerability – there are better tradeoffs in our view. At twelve weeks, cetilistat produced 3 to 4 kg of weight loss, or twice as much as placebo, and while the drug produced more GI side effects than placebo, the ~20% rate of withdrawal due to adverse events was not higher for the drug than placebo. In our opinion, cetilistat might make a good competitor against GSK's over-the-counter orlistat (Alli) but the modest efficacy might well prevent it from approval. That said, we are always surprised how high sales are of sibutramine (Abbott's Meridia) and orlistat (Roche's Xenical); together, the two achieved ~$1 billion in sales for 2006. As we understand it, publicity over rimonabant is fueling demand even for sub-optimal drugs.
- *JAMA - Comparison of the Atkins, Zone, Ornish, and LEARN Diets - Gardner et al:* This 12-month trial tested four popular weight-loss diets in 311 overweight or obese non-diabetic women. Participants were randomized to a diet, given weekly diet lessons for two months, and then followed up for the remaining ten months. Women lost 4.7 kg on the Atkins diet, 1.6 kg on the Zone diet, 2.6 kg on the LEARN diet, and 2.2 kg on the Ornish diet. The authors conclude that while questions remain about the long-term effects and mechanisms of a low-carb, high-protein, high-fat diet, it does appear to be the best choice for weight loss.
- *JAMA - Aging, Adiposity, and Calorie Restriction - Fontana, Klein:* In animals, calorie restriction decreases the risk of chronic diseases including diabetes, CVD, and certain cancers and increases longevity. This meta-analysis of calorie restriction in humans concludes that it produces beneficial metabolic, hormonal, inflammatory, and functional changes similar to those in rodents and monkeys. However, these are only intermediate measures, and no true outcomes studies have shown reduced clinical endpoints in humans yet.
- *JAMA - Geographic Disparities in Diabetes-Related Amputations--Texas-Mexico Border, 2003 - CDC:* Rates of lower extremity amputations (LEAs) are estimated to be a stunning 15 to 40 times greater among people with diabetes than those without. In Texas, the prevalence of diabetes is higher near the Mexico border, where residents tend to have worse health outcomes, be less educated, and have poorer health insurance. The CDC reports that the rate of diabetes-related LEAs is twice as high

near the border even after adjusting for age and sex: 53.6 per 10,000 persons in border counties versus 39.9 per 10,000 persons in non-border counties.

- *JAMA - Reasons for No Health Insurance Coverage Among Uninsured Persons Under 65 - CDC:* This sobering piece shows that 17% of people under 65 years have no health insurance. The reasons cited are: cost (53.3%), lost job or change of employment (26.9%), employer did not offer or insurance company refused (14.1%), Medicaid benefits stopped (10.0%), ineligible due to age or leaving school (6.2%), change in marital status or death of parent (28%), or other (6.0%). We agree with Dr. David Matthews of the UK who said at the recent Novo Nordisk forum that the US should be mortified that it is allowing this problem to persist and actually, to worsen.
- ***Lancet - Trends in Diabetes Prevalence, Incidence, and Mortality in Ontario, Canada 1995-2005 - Lipscombe, Hux:* The prevalence of diabetes in Ontario rose from 5.2% in 1995 to 8.8% in 2005 – an increase of 69% over ten years, or 6.2% each year. This is far higher than the WHO's prediction that the global prevalence of diabetes will rise 60% from 1995 to 2030, as well as the CDC's prediction that diabetes in the US will double from 2005 to 2050. We have thought previous estimates of prevalence increases were low, given, for example, that in the US it is estimated that between 1 and 1.5 million patients are diagnosed each year with diabetes while a far fewer number actually die.
- ***Lancet - Targeting High-risk Populations in the Fight Against Diabetes - The Lancet:* In an accompanying editorial to Lipscombe and Hux's paper, *The Lancet* reminds readers of the importance of global control of diabetes. They encourage putting regular screening programs for diabetes in place everywhere and propose that diabetes care be tailored to specific cultural groups because a "one-size-fits-all" approach isn't appropriate for a disease that affects different populations differently. They call on every country to develop a customized approach to care that is appropriate for its ethnic constituency. We couldn't agree more.
- *Lancet - Clinical update: the Low Glycaemic-index Diet - Ludwig:* This commentary on low glycemic index diets by category expert Dr. David Ludwig concludes that most published studies report beneficial effects of a low glycemic index diet and virtually no study suggests potential for harm (by contrast with low-fat and very-low-carbohydrate diets that can adversely affect some risk factors for cardiovascular disease). Pending results of more studies, he suggests that clinicians should consider a low-GI diet for the prevention and treatment of diabetes, heart disease, and obesity.
- *Nature Medicine - Beta-cell ABCA1 Influences Insulin Secretion, Glucose Homeostasis and Response to TZD Treatment - Brunham et al:* Abca1, a cellular cholesterol transporter, is necessary for normal β-cell functioning in mice. The researchers suggest that Abca1 prevents improper cholesterol accumulation in β-cells, which can cause cell death. This is an interesting hypothesis because it links dyslipidemia and insulin resistance, two problems that often occur together in the metabolic syndrome. An accompanying editorial by Chakravarthy and Semenkovich suggests that the treatment of diabetes and atherosclerosis could be simplified by targeting this single cholesterol pathway to treat both. The authors showed that rosiglitazone does a good job of just that – this is controversial, of course, due to side effects.

Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, Zinman B. "Impaired Fasting Glucose and Impaired Glucose Tolerance: Implications for care." Diabetes Care. March 2007. 30:753-759.

Main takeaways: *1)* ***This statement is conservative and recommends metformin as the only drug therapy for IFG/IGT patients****. We find this position unsurprising considering the safety issues associated with TZDs, which are currently the only drugs with comparable efficacy to lifestyle intervention in preventing diabetes. The FDA recently issued a statement (March 8) informing doctors that pioglitazone is also associated with increased risk of fractures, indicating that the ADOPT findings were a class effect. This further adds to their considerable tolerability*

and safety issues. 2) ***This might represent an opening for incretins, especially GLP-1-based therapies, though this panel is clearly a tough audience and not many studies are being done here yet (incretins for pre-diabetes) – that are public, anyway****. We believe this panel will require very strong clinical evidence (long-term, large, randomized-controlled trial) of both benefit and safety comparable to lifestyle intervention before they are likely to recommend a branded drug for diabetes prevention – we don't know of any in the works, but some oft-mentioned potential candidates for such trials include exenatide LAR, rimonabant, and the DPP-4 inhibitors.*

This paper reports the results of an October 16-18, 2006 consensus panel on prediabetes. At this meeting, the seven authors, who are thought leaders in diabetes and metabolism, together developed this consensus statement on what IFG and IGT are and how to treat them. The statement begins with an extensive discussion of what IFG and IGT are, in which it is noted that the majority of patients with either diagnosis will eventually progress to outright diabetes, though the exact rate of progression is unclear. The panel notes that the natural history of IFG/IGT and whether we can alter it ARE unclear.

There are three ways of defining the natural history of IFG/IGT and two ways to alter it. The natural history of IFG/IGT can be measured 1) by progression to diabetes, 2) by changes in underlying defects such as insulin secretion and insulin resistance, or 3) by the development of complications such as microvascular and macrovascular disease. Altering the natural history of IFG/IGT can be done either through a treatment that "resets the clock" by delaying hyperglycemia without actually changing the rate of progression of underlying defects, or through a treatment that treats the underlying pathophysiology of disease, perhaps by slowing the loss of β-cell function or decreasing insulin resistance. The authors write that no trials have definitively shown whether specific interventions do the former or latter. We would suppose that lifestyle intervention does the latter, whereas the case for TZDs is less clear, and incretins, DPP-4 inhibitors, and rimonabant have yet to be studied in this context.

Their recommendations are, perhaps unsurprisingly, very conservative: while the authors write that they believe "in principle that early intervention is justified" based on the potential to postpone the onset and treatment of diabetes as well as preserving β-cell function and delaying complications, they recommend weight loss (5-10% of body weight) and moderate physical activity (at least 30 minutes daily) as the primary treatment for people with IFG and IGT. We absolutely agree with this as early therapy and just note that people tend to get "stuck" when they can't achieve these goals – diabetes often ensues.

The only pharmacotherapy option that they recommend for IGT/IFG patients is metformin, and then only for people under 60 years old and with BMI over 35 kg/m^2 – a population that precludes the thinner type 2 patients whose pathophysiology has more to do with loss of b-ell function than insulin resistance (older patients and Asians come to mind). While other options are discussed – acarbose (Bayer's Precose), orlistat (Roche's Xenical), and rosiglitazone (GSK's Avandia) – all three are dismissed because of tolerability and safety issues. While the authors acknowledge that obesity is a primary contributor to IFG/IGT and that obese patients should be encouraged to lose weight, they do not mention pharmacotherapy options for weight loss. Rimonabant is not mentioned, nor are the incretins, which makes sense since these drugs are newer, expensive, and unproven so far. However, we think the omission speaks to the conservative nature of this panel (Dr. Nathan being the lead author).

We hope that more studies are done so that evidence is created to show efficacy or lack thereof for other drugs. While the TZDs certainly do have their tolerability issues and are associated with fractures *and* congestive heart failure (CHF), we found the DREAM data compelling enough to think that they should perhaps have at least a small place in the pantheon of diabetes prevention – or at least that they should be studied further (see our Takeda company update on page 11 for a note on fractures).

This might represent an opening for incretins, especially GLP-1-based therapies, though this panel is clearly a tough audience and not enough studies have been done to provide a good evidence base. For any potential newer drugs for diabetes prevention (like rimonabant, exenatide, LAR, or the DPP-4 inhibitors), we believe that well-designed and successful outcomes trials will take many years. A

DREAM-like trial with exenatide LAR or any of these options would be exciting, particularly if the evidence were positive – and we could prevent this disease – but we aren't holding our breath for any such trial to begin.

—by Jenny J. Jin and Kelly L. Close

9. Upcoming Conference Previews

- **Prediabetes Congress, April 25-28, Barcelona, Spain http://www.kenes.com/prediabetes/**

  The 2nd International Congress on Prediabetes and the Metabolic Syndrome will be, we believe, one of the most important of the year. A stellar cast of speakers and presentation topics will be featured. Below we present our top picks of events to attend, grouped by category: satellite symposia, plenary sessions, parallel sessions, and poster sessions.

  Satellite Symposia

  On **Wednesday**, April 25, the "International Chair on Cardiometabolic Risk," an independent academic forum that sanofi-aventis established to focus care on cardiometabolic risk, will be kicking off the meeting with an amazing symposium full of expert speakers on "*Abdominal Obesity, Metabolic Syndrome and Global Cardiometabolic Risk*" at 11:00-13:00. Dr. Rury Holman of the University of Oxford (who has been involved in many of the most important outcomes trials over the last decades) and Dr. Philip Barter of the Heart Research Institute in Sydney will chair the session. Additional speakers include Dr. Paul Zimmet of the International Diabetes Institute in Australia, Dr. Luc Van Gaal of Antwerp University, Dr. Richard Nesto of Lahey Clinic in Burlington, MA, and Dr. Jean-Pierre Despres of Universite Laval in Quebec. This is an outstanding teaching group.

  Afterwards, Novo Nordisk will sponsor a symposium on "*Central Nervous System, Endocrine and Cardiovascular alterations in Prediabetes*" at 13:30-15:30, chaired by highly regarded complications expert Dr. Michael Brownlee from New York and including a talk by incretin expert Dr. Jens Holst of the University of Copenhagen on GLP-1's role in the postprandial state. In the evening, Dr. Rury Holman will chair another symposium, this one sponsored by Bayer Schering Pharma AG, on "*Entering a new era of diabetes and cardiovascular disease prevention*" at 16:00-18:00. Speakers will talk about the link between hyperglycemia and CVD and the role of acarbose in prevention. Merck Serono will also sponsor a symposium at the same time chaired by Dr. Ian Campbell from Scotland on "*Diabetes prevention – low-risk intervention strategies for high-risk patients*."

  On **Thursday** night at 8:15-20:15, two very interesting symposia will commence on TZDs and DPP-4 inhibitors, respectively, for diabetes prevention. MSD (Merck) will sponsor a symposium chaired by Dr. Ramon Gomis from Spain on "*Incretins and the natural history of Type 2 Diabetes: Current utility and potential for DPP-4 inhibitors.*" Speakers include Dr. Ele Ferrannini from University of Pisa, Dr. Tina Vilsboll from University of Copenhagen (whom we know from so many other talks to be at the top of her game – look out next issue for conference notes featuring Dr. Vilsboll from Diabetes UK), and Dr. Pablo Aschner from Javeriana University. GlaxoSmithKline will sponsor a symposium chaired by the savvy Dr. Bernard Zinman of Toronto titled "*Can we delay disease progression in patients with hyperglycemia? Latest evidence and clinical insights.*" It will include talks from Dr. Hertzel Gerstein, Dr. Richard Nesto, Dr. GianCarlo Viberti, and Dr. Rury Holman.

  Finally, two more incretin-focused symposia on **Friday** night will round out the corporate-sponsored presentations. At 8:15-20:15, Lilly will sponsor a symposium on "*Incretin Mimetics: New Dimensions in Diabetes Care.*" Speakers include Dr. Rury Homan and the noted Dr. Robert Ratner of the Medstar Research Institute. Simultaneously (which is why two of our team will be attending), Novartis will sponsor a symposium chaired by fantastic educator Dr. Julio Rosenstock on "*Islet enhancement through DPP-4 inhibition as a treatment target in Prediabetes*." Speakers include Dr. Rosenstock as well as basic scientist Dr. Daniel Drucker from University of Toronto.

Plenary Sessions

The official congress program will begin on **Wednesday** night with an "*Opening Session*" chaired by Dr. George Alberti from London and Dr. Pesach Segal from Israel. Speakers include Dr. Paul Zimmet and metabolic syndrome expert Dr. Scott Grundy of the University of Texas.

Thursday's opening plenary session at 8:30-10:30 is titled "*Setting the Scene – Definitions and epidemiology*," in which Dr. Paul Zimmet will clarify the topic of the metabolic syndrome and Dr. Robert Eckel will discuss pathophysiological mechanisms and clinical options for prediabetes and the metabolic syndrome. The Friday evening plenary session is packed with fine speakers. It will take place at 16:00-18:00 and is titled "*Emerging metabolic therapies.*" Dr. Harold Lebovitz of SUNY Brooklyn and Dr. Rury Holman will chair a roster of speakers that begin with Dr. Jens Holst of University of Copenhagen on GLP-1 and DPP-IV inhibitors, followed by Dr. David Moller from Lilly on new approaches to insulin sensitization. Dr. Paul Steward of University of Birmingham will discuss 11-beta hydroxysteroid dehydrogenase inhibitors, Dr. Franz Matschinsky of University of Pennsylvania will discuss glucokinase activators (GKA), and Dr. Michael Czech of University of Massachusetts, Worchester, will finish with a talk on an RNA interference-based drugs.

Friday's opening plenary session at 8:30-10:30 is titled "*Hyperglycemia and heart disease,*" chaired by Dr. Lars Ryden from Sweden and Dr. Richard Nesto. The speakers include clinical experts such as Dr. Scott Grundy of University of Texas, Dr. Greet Van Den Berghe of K.U. Leuven (known for her in-hospital tight glycemic control), Dr. Klaus Malmberg from Stockholm, Portland Protocol powerhouse Dr. Anthony Furnary from Oregon, and Dr. Eberhard Standl, Vice President of the IDF. Dr. Paul Zimmet and Dr. Manuel Rios from Spain will chair the evening plenary session at 16:00-18:00, titled "*Preventing Diabetes Mellitus with gluco-metabolic interventions in people with dysglycemia – the evidence*." Dr. Bernard Zinman will speak on combination therapy, and Dr. Ralph DeFronzo of University of Texas will discuss future directions in diabetes prevention.

Saturday's plenary session will conclude the congress with a session on "*Partners in Prevention*" at 12:15-14:00. We look forward to a talk on the role of the food industry at 12:55 and another on responsibilities and opportunities for industry in the diabetes epidemic at 13:15. Dr. Paul Zimmet will give the closing remarks for the congress.

Parallel Sessions

There will be two excellent parallel sessions on **Thursday** at 11:00-12:30. The first, on "*Global risks and consequences of Prediabetes/Metabolic Syndrome,*" will include international speakers from China, India, and one of our favorite speakers, Dr. Jean-Claude Mbanya from Cameroon – anyone who is there to hear him is in for a treat. The second, on "*Physiologic abnormalities associated with the Metabolic Syndrome*," features presentations on adipokines and endothelial function, as well as a talk from Dr. Ralph DeFronzo on insulin resistance, atherosclerosis, and type 2 diabetes. In the afternoon, we'll be looking forward to hearing the famous Dr. Stephanie Amiel of Kings College talk about regional brain insulin resistance in metabolic syndrome at 14:00 in a session on "*Cerebral manifestations of the Metabolic Syndrome*" as well as hearing Dr. Michael Brownlee talk about insulin resistance in proatherogenic endothelial changes at 15:00 in a session on "*Mitochondrial mechanisms and the Metabolic Syndrome, Prediabetes, and Diabetes Mellitus.*"

On **Friday**, we're looking forward to hearing Dr. Bart Staels talk about PPARs at 11:20 at a session on "*Cellular mechanisms and the Metabolic Syndrome, Prediabetes, and Diabetes Mellitus*." From 11:00-12:30 there will also be an interesting session on "*Abdominal obesity*" chaired by obesity expert Dr. Louis Aronne from Cornell and Dr. Luc Van Gaal from Belgium – clearly relevant to rimonabant. In the afternoon we'll want to hear Dr. Jorge Plutzky talk about the effect of TZDs on vascular function at 14:20 in a session titled "*Vascular effects of gluco-metabolic therapies*." From 14:00-15:30 there will also be an extremely exciting session on "*Emerging new treatments of obesity*"

with not-to-be-missed speakers: Dr. Louis Aronne, Dr. David Cummings from Seattle, Dr. Steven Bloom of Imperial College London, and Dr. Harold Lebovitz from Brooklyn.

Parallel sessions begin early on **Saturday**. At 8:30-10:00, we look forward to Dr. Rury Holman and Dr. Steven Kahn's talks on metformin and TZDs respectively for cardiovascular disease prevention in a session titled "*Do gluco-metabolic interventions prevent Cardiovascular Disease?*" Simultaneously, Dr. Jay Skyler will be chairing an important session on "*Prediabetes/Metabolic Syndrome in the young,*" which will include talks by Dr. Francine Kaufman of USC and Dr. Sonia Caprio of Yale. At 10:30-12:00 we plan on racing to the session on "*Does targeting treatment to individual components of the Metabolic Syndrome reduce Cardiovascular Risk?*" It will include talks from Dr. Henry Ginsberg of Columbia University, Dr. Antonio Ceriello of University of Warwick, well known for all his work on glycemic variability, and Dr. Jay Skyler of University of Miami.

Poster Sessions

Thursday's poster session on "*Therapy*" will include a short presentation at 11:10 from Dr. Tina Vilsboll on what looks like the 14-week liraglutide study she also presented at Diabetes UK, followed by an Amylin/Lilly poster presentation by Dr. T. Okerson on 2.5-year exenatide data at 11:20. Friday's poster session on "*Adipokines and inflammatory/stress markers*" will begin with a presentation from Dr. Stefan Soderberg on leptin's link to diabetes. Saturday's poster session on "*Heart and vascular*" will conclude with a presentation from Dr. Amir Tirosh on diabetes and CAD prediction in adolescents at 9:45. We look forward to attending the poster prize award session as well, at 12:00-12:15 on Saturday.

Now, can you imagine missing this conference? We can't! Please let us know if you'll be there as we're planning a fun night of paella, details to be confirmed, but if you can come, be in touch (kelly@closeconcerns.com).

- **Children With Diabetes, July 11-15, Lake Buena Vista, Florida http://www.childrenwithdiabetes.com/activities/Orlando2007/**

  This is truly one of our favorite meetings of the year, a huge gathering with first-rate faculty, cutting-edge information, and a massive exhibit hall – and it's for patients! That said, anyone who works in the field can learn as much or more at this conference than at many scientific meetings. Children With Diabetes is a large online forum for families dealing with diabetes. In 2000, an informal suggestion on the message boards to meet for a fun vacation brought 550 people to Disneyworld. A great idea was born, and this year's meeting (the eighth annual) is expected to bring 2,500 people. Laura Billetdeaux, who made the initial suggestion and who now does much of the planning, expects this year to be the first conference to sell out.

  Like many meetings (and vacations), it isn't inexpensive. Registration for a family of four (including a special banquet and breakfast) is $490, and rooms cost $141 per night – not to mention tickets to Magic Kingdom (many go on the last full day) as well as travel costs. Speaking of which: last year we met a family from Poland with a diabetic teenager; the father runs a video store in Warsaw.

  The great excitement last year occurred when Kevin Covais, an American Idol star with type 1 diabetes, showed up and performed after the big Thursday evening banquet, and he plans on making an encore appearance this year as well.

  The meeting has terrific corporate sponsorship – Roche sponsors the Grand Opening Ceremony, Lilly sponsors a lunch buffet, Abbott sponsors a "Magical Memories Breakfast" (where you eat breakfast with Disney characters), Sanofi sponsors a lunch buffet, Novo Nordisk sponsors a "Fun Run" and a breakfast buffet, Novo Nordisk and LifeScan jointly sponsor the Family and Friends Banquet and the music and dancing that follows, LifeScan sponsors a breakfast and a "tweener social," Animas sponsors gratis childcare for those too young to go to the meetings, Smiths Medical sponsors two

snack breaks, BD sponsors dessert with faculty, Unomedical sponsors a Teen Dinner Dance, Animas sponsors a day at the Magic Kingdom with CDEs on staff at the park, and Medtronic sponsors the Farewell Breakfast. Below we highlight some exciting speakers:

There are several tracks throughout this meeting, though some are just for teens or even elementary-age children. We expect everyone will come together to hear Dr. Kenneth Moritsugu, the US Surgeon General, who will deliver the keynote speech – a real coup. When Laura Billetdeaux spoke to us, she said she plans to put him on a panel with teens, college students, and parents to discuss their hopes and concerns about diabetes – how incredible is that? There are several sessions for "parents & adults only" that we plan on attending. Joe Solowiejcyzk is a family counselor focused on diabetes education and speaks on "Family Dynamics for Parents of Kids Ages 0-11" and then again for parents of kids ages 12 to 17. Paul Madden, now of Animas and formerly from the Joslin Diabetes Center, discusses "*Making it All Work: the Force is with You*." The rest of the top-notch sessions are split between practical advice and research sessions. On the practical front, some of our favorite experts will give advice for living with diabetes: including Dr. Henry Anhalt on "*Why We Pump*," Dr. Bruce Buckingham on "*Maximizing MDI*," Scott Scolnick, an Animas regional manager, on being "*Angry at Diabetes,*" Dr. Irl Hirsch on "*Understanding the Ups and Downs of Blood Sugar*," Dr. Richard Rubin, outgoing President of Health and Education at the ADA, on the condition of "*Diabetes Overwhelmus*," and Dr. Francine Kaufman on "*Healthy Living for People with Type 1 Diabetes*."

And then there are those cutting edge research sessions: Dr. David Harlan, Chief of Islet and Autoimmunity research at the NIDDK, gives an "*NIH Research Update*," John Walsh, a CDE, talks about "*Advanced Pumping Concepts*," Dr. Kaufman discusses "*Double Diabetes in Kids*," a growing problem, as well as "*Pregnancy and Diabetes*," and Dr. Norma Kenyon, Chair of Diabetes Research at the University of Miami, gives a "*DRI Research Update*." Dr. Buckingham talks about "*Continuous Glucose Sensing*," Dr. Hirsch discusses "*The Future of Treating Type 1 Diabetes,*" and Dr. Aaron Kowalski, who leads the Artificial Pancreas Project at the JDRF, talks about the artificial pancreas along with Dr. Stuart Weinzimer, of the Yale School of Medicine, and Dr. Edward Damiano, a professor of Biomedical Engineering at Boston University.

—by Daniel A. Belkin, James S. Hirsch, Jenny J. Jin, and Kelly L. Close