DIABETESCLOSEUP

*The Leading Source of Diabetes Business News*

**Hail, Valentino!** **April 2008 • No. 79**

## From the Editor

*On Tuesday, March 25, 2008, at 3:17 p.m., my husband, John, and I were thrilled to welcome a new little baby into our world. Our son was born very early – at 30 weeks[1] – and we are very lucky to be able to say that he has been progressing well. We feel fortunate, as you would imagine. We would like to thank everyone for all your good vibes, powerful prayers, amazing flowers, considerate phone calls, delightful email messages and much-appreciated visits (including four readers who came to have dinner with us at the University of California at San Francisco while I was on bedrest[2]).*

*The main job of a tiny newborn is just to grow, and our little son is growing every day, for which we are grateful. While he is still in the neonatal ICU at UCSF, where he will be for about five or six more weeks, he soon will graduate, we hope, into a "feeder and grower," as they say in the NICU.*

*One challenge, of course, was settling on the right baby name, one that would complement the names of our first two children, Coco and Lola. We cycled through a wide range of options – from Aloysius to William – but finally chose one that, translated, means "strong, healthy."*

Hail, Valentino!

*We think it's perfect. Please keep your good luck flowing our way.*

*Switching gears, if that is possible, we want to say how much we're looking forward to seeing so many of you at ADA in June here in San Francisco. We hope you will join us in supporting the amazing Taking Control of Your Diabetes organization, led by Dr. Steve Edelman, who has type 1 diabetes himself and who gives so much to all us patients and providers and manufacturers. I will be moderating the second annual TCOYD Diabetes Forum that includes an incredible panel: Dr. Edelman, Dr. Wayman Wendell Cheatham, Dr. James Gavin, Dr. Robert Henry, Dr. Anne Peters, and Dr. Eugene Wright (PCP expert!).*

*The Q&A will be fast-paced, and will focus on current and next-generation GLP-1 and DPP-4 inhibitors, CGM acceptance and reimbursement, next-gen insulin delivery, compounds in basic and clinical research (PTP1b inhibitors, SGLT-2 inhibitors, 11bHSD, SPPARMs), bariatric surgery, etc. "Where do I sign up?!" This will be at the Westin St. Francis on Sunday, June 8 – sign up at www.supporttcoyd.org. One hundred percent of donations go to patient education for people with diabetes. The event will begin at 5 p.m. with cocktails and snacks, followed by a panel discussion and a Q&A session.*

*To close, from John, Coco, Lola, Valentino, and myself, we say:*

*Thank you,*

*Kelly L. Close*

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[1] *Some of you have asked why diabetes can cause early delivery – it doesn't – we understand this was just bad luck…*

[2] *Eating Thai takeout, albeit with Guinness – that is friendship!*

## Major Headlines



## In This Issue



## Blogwatch

See below for blogs since our last monthly newsletter. You can view all of our blogs and subscribe to the RSS blog feed online at www.closeconcerns.typepad.com/close_concerns_weblog/

- **April 25:** What! What do you mean someone with diabetes can't be healthy?! The New York Times!
- **April 14**: Type 2 diabetes, reinvented
- **April 4**: Good weather's coming, dust off those walking shoes for a good cause
- **April 3**: Taranabant – Not a magic bullet
- **April 2**: Take me out to the ballgame… or buffet?

## Coming soon in DCU

The weather is warming up, and the ADA 68th Scientific Sessions feel like they are getting close! While ADA has always been a highlight for us, this year's meeting looks to be especially exciting and data-rich. In the next issue of Diabetes Close Up, we'll bring you our annual comprehensive ADA preview. Notes from AACE, where we are headed in a couple of weeks, will follow soon after, along with an update from the 16th Annual Congress on Obesity in Geneva.


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## 1. Quotable Quotes in Diabetes

*"We spend all this time railing against the evils of the obese state and then we turn around and give them therapies that make them gain weight, making us look completely and utterly incompetent."*

— Dr. Alan Garber of Baylor College of Medicine in Houston, Texas, speaking at the Fourth Annual Clinical Diabetes Technology Meeting about the need for incretin therapies such as Byetta that are weight neutral or cause weight loss.

*"Do all diabetics need a statin? No... but almost all do."*

—Dr. Steven Haffner of the University of Texas Health Science Center and Dr. Jack Leahy of the University of Vermont expressed agreement in a panel at the 57th Annual Scientific Session of the American College of Cardiology that most people with diabetes should use a statin.

*"The next frontier will be beyond our concepts and tools, and cardiologists will need to expand their role in the management of diabetes and metabolic derangements."*

— Dr. Richard Nesto, Chairman of Cardiovascular Medicine at the Lahey Clinic Medical Center in Burlington, MA, and Associate Professor of Medicine at Harvard University, on the blurring line between endocrinology and cardiology at the 57th Annual Scientific Session of the American College of Cardiology.

*"Multiple compounds in this space have had problems, so it is important that we evaluate each compound separately given the unknown genetic effects of each drug. Pioglitazone right now appears to have the right constellation of factors needed to have beneficial effects."*

— Dr. Steven Nissen of the Cleveland Clinic, underscoring that the positive effects of Actos observed in the PERISCOPE study cannot be extrapolated to Avandia, during his presentation of the study results at the 57th Annual Scientific Session of the American College of Cardiology.

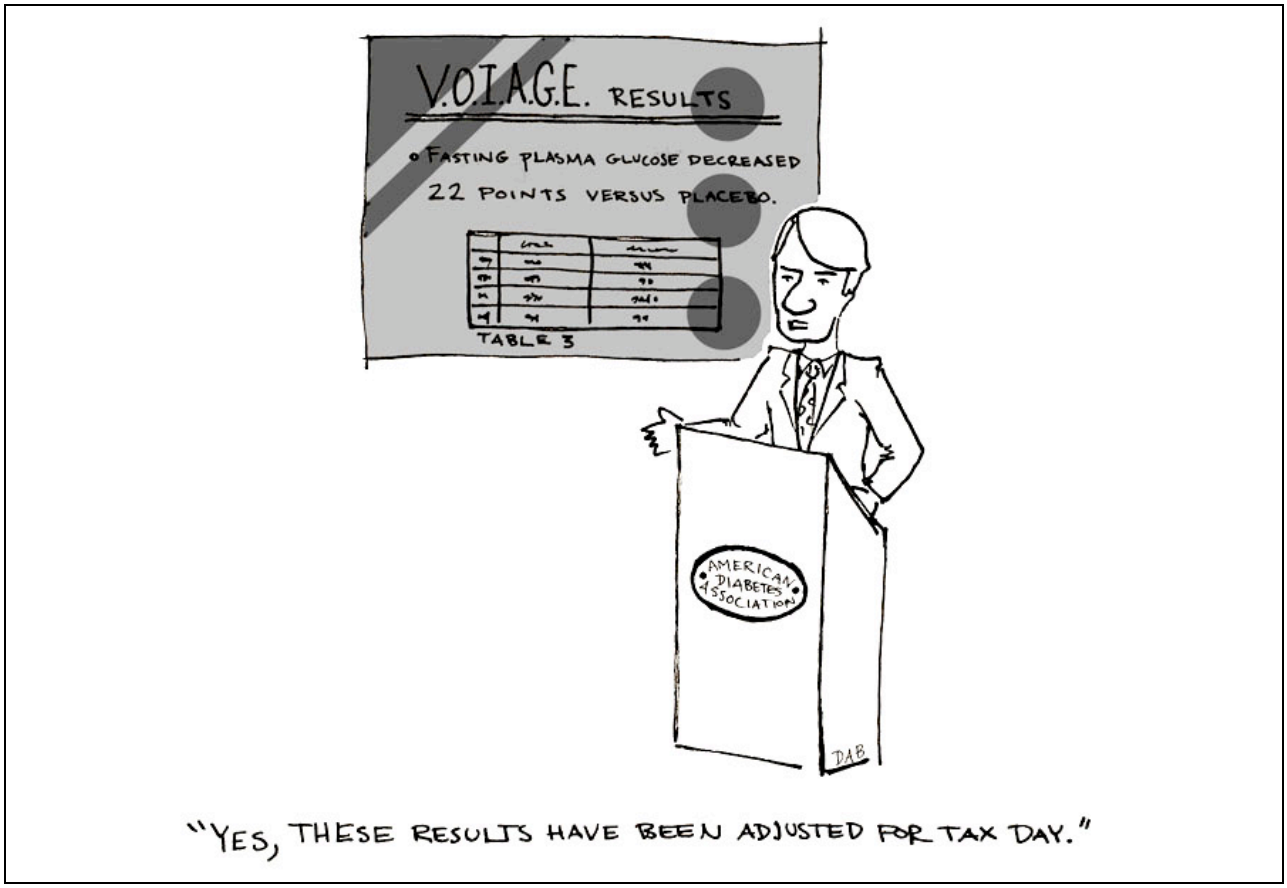
*"The availability of U-500 insulin now makes it easier to administer the doses of insulin necessary to overpower insulin resistance. But is it rational to overpower resistance to insulin without eliminating the caloric excess that created the abnormalities? [Overpowering] insulin resistance may be harmful, quite possibly because doing so forces lipogenesis and promotes ectopic deposition of lipids."*

— Dr. Roger H. Unger of the Touchstone Center for Diabetes Research, University of Texas Southwestern Medical Center, putting forward a lipocentric view of diabetes in a commentary entitled "Reinventing Type 2 Diabetes," which was published in *The Journal of the American Medical Association* on March 12.

*"With the large number of annual visits for hypoglycemia and the majority (75%) resulting in discharge, the emergency department should be an important venue for education and referral."*

— Dr. Adit A. Ginde and colleagues, reviewing trends in emergency department visits for hypoglycemia in a piece entitled "Trends and Disparities in U.S. Emergency Department Visits for Hypoglycemia, 1993–2005," which was published in the March issue of *Diabetes Care*.

## 2. diaTribe FingerSticks




*-by Daniel A. Belkin*

## 3. DCU Company Watch

- **BMS/AZ—Saxagliptin filing expected mid-2008:** On April 24, Bristol-Myers Squibb and AstraZeneca both reported 1Q08 earnings and provided a brief update on the development of saxagliptin and dapagliflozin, the two drugs they are working on together. As a reminder, saxagliptin is a DPP-4 inhibitor in phase 3, and dapagliflozin, which is currently in phase 2, is poised to be the first-in-class SGTL-2 inhibitor. Both companies briefly mentioned that the saxagliptin filing is "on track" for mid-year; saxagliptin was set to be filed in 1H08, so as long as mid-year means "by the end of June" nothing has changed. Otherwise, this likely represents a bit of a delay, though not a major one. If saxagliptin is filed mid-year, it could become the third DPP-4 inhibitor on the market, after Merck's Januvia and Takeda's alogliptin, which was filed in January of this year. We also learned that phase 3 data for saxagliptin and phase 2 data for dapagliflozin will be presented at ADA in June, with additional phase 3 data for saxagliptin presented at EASD in September. With seven SGLT-2 inhibitors in clinical development (to the best of our knowledge), the presentation of phase 2 data for dapagliflozin will be one of the first opportunities to assess the future of this new drug class. We'll be especially watchful for the side effects of dapagliflozin, as some have speculated that SGLT-2 inhibition may be mechanistically linked with polyuria (frequent urination, including in the middle of the night) and urinary tract infections. This is because increased glucose in the urine increases the amount of nutrients for

bacteria in the urinary tract, leading to higher bacteria counts and potentially increased urine tract infection rates. The frequent urination associated with polyuria is due to the increased volume of water pulled into urine through osmosis given the high glucose concentration.

- **GSK/Sirtris—GSK intent on purchasing Sirtris for $720 million, an 84% premium:** On April 22, GSK announced that it made a $720 million all-cash offer for Sirtris Pharmaceuticals ($22.50 a share), a sizable 84% premium over the company's last valuation of $12.23 a share. The acquisition was approved by the board of directors of both Sirtris and GSK, and is expected to close in 2Q08. Under the plan, Sirtris will continue to operate independently with its current leadership.

  Given GSK's difficulties with Avandia, the move by GSK to further diversify its diabetes portfolio makes sense. With this acquisition, GSK will have lots in its diabetes pipeline, including an SGLT2 inhibitor (remogliflozin, partnered with Kissei Pharmaceuticals), a long acting GLP-1 (albiglutide, partnered with Human Genome Sciences), and several PPARs. We believe that GSK management likely made the decision to go all out to acquire the company now in order to pre-empt other competitors from acquiring Sirtris. Sirtris went public in May 2007 for $10/share. Assuming that GSK's acquisition of Sirtris is completed, we expect that monitoring Sirtris's drug development progress will become more difficult. Notably, the acquisition wasn't mentioned during the GSK 1Q08 earnings call a day after the bid was announced. In some respects, we are surprised by how early the Sirtris board agreed for the company to be acquired, though with the brainpower at GSK, that would be a very hard offer to turn down. We believe that that GSK's deep pockets will enable Sirtris to accelerate its research and development of SIRT3, another sirtuin believed to be a target for the treatment of metabolic diseases. What remains to be seen is whether Sirtris will continue to develop SRT-501 (currently in phase 2), or will wait for its more potent NCEs that are currently in preclinical testing. We expect that Sirtris will wait for the phase 2a results for SRT-501, due later this year, to make this choice.

  Less than a week before GSK's bid for the company was announced, Sirtris reported top-line data for its second phase 1b study of SRT-501. This study was very similar to the company's first phase 1b study, the main difference being twice daily rather than once-daily dosing. Results were unsurprising but overall positive in our view. Similar to the company's first phase 1b study, the higher dose of SRT-501 significantly lowered blood glucose levels as shown through an oral glucose tolerance test (OGTT) at the test's two-hour time point. Safety data were also encouraging, as no drug-related adverse events were noted. In the present study, fasting glucose was also significantly lowered (whereas in the first phase 1b study, there was a "trend" toward glucose lowering), suggesting that twice-daily dosing is likely more effective than once-daily – of course, we would like to see the full data set before drawing this conclusion. The full phase 1b data will be presented at the ADA in June. In our view, the main implications of this study are 1) further validation of the mechanism, 2) more evidence of drug safety (at this point ~180 patients have been dosed with SRT-501), and 3) possible support for twice-daily dosing as opposed to once-daily dosing.

- **Vivus—All three Qnexa phase 3 clinical trials are fully enrolled ahead of schedule:** On April 22, Vivus announced that it had completed enrollment of the last of its three Qnexa phase 3 clinical trials: EQUATE (OB-301), EQUIP (OB-302), and CONQUER (OB-303). The enrollment timing is somewhat ahead of schedule. EQUATE (OB-301) is a 28-week, 700-patient randomized controlled trial with subjects who have BMIs ranging from 30 kg/m$^2$ to 45 kg/m$^2$ (this includes the lowest end of obese, since overweight BMI is 25-29.9 kg/m$^2$). EQUIP is a 56-week study that is enrolling 1,250 morbidly obese patients with BMI that equals or exceeds 35 kg/m$^2$. CONQUER is a 56-week study enrolling 2,500 patients with BMIs ranging from 27 kg/m$^2$

to 45 kg/m² and two related co-morbidities. We are especially interested to see the side effect data from these trials, given the rather concerning monotherapy data for topiramate (increased risk of suicidality). Vivus has previously argued that phentermine will offset many of the side effects of topiramate (for example, topiramate is a depressant and phentermine is a stimulant.) Results for the 4,500 subject phase 3 program are now expected in mid-2009.

- **Amylin—Byetta sequential sales flat, waiting for exenatide once-weekly news:** During Amylin's 1Q08 on April 22, management announced that Byetta sales had slipped to $158.5 million, from $176 million in 4Q07. After adjusting for the $10-12 million in wholesales stocking announced last quarter and a drawdown this quarter, sequential sales were basically flat. Amylin management acknowledged that Byetta was not growing as quickly as it should, and that execution was not where management would like to see it. To address this, at least in part, Amylin will increase its sales force by 15% to better target high-prescribing PCPs, where Byetta prescriptions are currently weaker than expected. CEO Daniel Bradbury noted during the call that 80% of diabetes prescriptions are now written by PCPs, while a disproportionate number of early adopters and Byetta prescribers are specialists.

  On a more positive note, the Byetta monotherapy submission has gone to the FDA. We believe given the continued move toward earlier, more aggressive therapy and earlier combination therapy it will be great for Byetta to have the monotherapy label. On the trial front, we look forward to impressive LAR superiority studies and believe this will drive significant demand, as long as the drug is easy to teach and to use. Amylin did not provide any news on its NDA submission for once-weekly exenatide. Timing is still set for "by first half 2009" though Lilly acknowledged on its 1Q08 call that an earlier submission was possible. Notably, Amylin is now manufacturing once-weekly exenatide at commercial scale and will introduce this material into clinical trials in 3Q08. That this material is being introduced in 3Q is good news in our view, as it reduces the risk that delays will emerge on the production front.

  Symlin sales increased to $20.2 million in 1Q08 from $18.4 million in 4Q07 and $15.5 million in 1Q07, benefiting from the SymlinPen launch. The SymlinPen now accounts for 39% of new Symlin prescriptions, and 21% of total Symlin use. Bradbury said that Amylin is working on new Symlin messaging involving the SymlinPen; the company now has pen-only sampling and a revamped website. This is a complex drug to take but has unique benefits in our view, and we believe uptake will continue to increase; this is very positive in terms of profitability since Amylin owns 100% of the drug. On the obesity front, management hinted briefly at possibly seeking partnerships for the development of its early-stage obesity candidates in order to reduce development expenses. Bradbury mentioned that Amylin continues to evaluate an “array” of peptide delivery options, and we were excited to hear about a partnership with Pacira and its technology platform DepoFoam. At ADA, Amylin and Amylin/Lilly will have 30 posters– we look forward to their Sunday night update during the meeting, and in particular, for four-year open label data on Byetta.

- **Lilly—Humalog sales impress, bolstered by KwikPen:** During Lilly’s 1Q08 earnings call on April 22, management announced that Humalog sales had grown to $407 million, a 20% increase from the same period a year before. Both new and total prescriptions were shown to have accelerated throughout the quarter. Presumably management offered this detail to show that not all the Humalog sales strength stemmed from KwikPen stocking. Lilly management did say in late 2005 that it would re-energize the insulin franchise, and Lilly has shown significant improvement since that time. Humalog’s growth since then has been especially impressive given the greater emphasis placed on long-acting analogs for type 2. Lilly announced renewed work with patient education this quarter and other initiatives, including DTC videos, and increased support for

diabetes advocacy groups. On the sales front, we note price increases have also helped, and Lilly has often said following a quarter's results that further insulin price increases won't be seen – but they continue to be, undoubtedly helped by the higher price ceiling of other diabetes drugs (TZDs, Januvia, and Byetta) that compete with insulin. All told, we would be surprised to see 20% increases in Humalog sales sustained, but we do believe this was a very good result following a fairly tough comparison: the 11% increase in Humalog sales a year ago. As we have written before, we continue to think Lilly would benefit from a long-acting insulin analog to pair with Humalog. Humulin sales were $258 million, up 14% from $226 million in 1Q07, and down approximately 6% from $274 million in 4Q07. We think the Humulin franchise is a good hedge against reimbursement woes, and 14% growth is impressive (this was an easier comparison, as 1Q07 sales for Humulin had risen just 3%). On the disappointing side, sales for Byetta slipped by approximately 10% from 4Q07. International sales for Byetta of $10 million continue particularly slowly; we believe it is a matter of resources and we will be interested to see how international progress unfolds..

- **Merck—Januvia sales continue to climb:** Januvia was not a major focus of Merck's April 21 earnings call, but the franchise did very well in Q1, posting revenue of $330 million, up 11% from 4Q07 and already annualizing at a blockbuster pace in its fifth full quarter on the market. Januvia sales rose 8% to $272 million from 4Q07, and Janumet sales increased 32% to $58 million. Januvia is the second biggest oral drug in the US behind Actos. We think it will be some time before Januvia could leap into the top spot, but for being out just 18 months, the current standing is certainly impressive. International sales for Januvia and Janumet were $48 million, double last quarter. The franchise has now been launched across Europe, in countries including France, Italy, and Spain.

- **Roche—1Q08 reflects US blood glucose monitoring weakness:** Roche's 1Q08 results on April 16 led by new CEO Severin Schwan reflected weakness in US blood glucose monitoring sales. Globally, Diabetes Care reported sales of CHF 699 million ($696 million using the current exchange rate of $0.996 per CHF). This reflects a sales decline of 7% (3% in local currency) from 1Q07. US revenue was reported at CHF 147 million ($146 million), down a striking 23% from 1Q07. Of note was a decline in North American revenue attributed to the impact of the new CMS competitive bidding program, which was reported to have affected orders from large accounts. Management expressed uncertainty with regard to this program; we think the CMS bidding represents another negative for the US market and that Roche is likely losing some share to competitors in the US in the blood glucose monitoring area. The market, of course, continues to increase due to the continued growth of the population of people with diabetes. Management did not review insulin pump results, which we understand declined year over year. Xenical sales fell 11% (local currency) globally at CHF 136 million ($136 million), and fell 35% (local currency) in the US from CHF 14 million ($14 million).

  On the drug front, management indicated that phase 2 analysis is complete for its GLP-1 analog and discussions with regulatory authorities are ongoing on the commencement and final design of phase 3 trials. Management was less vocal about its DPP-4 inhibitor program. Previously, Roche indicated that its DPP-4 inhibitor would likely be best-in-class and cause significant weight loss. From our perspective, unlike the GLP-1 analogs, the DPP-4 inhibitors are likely to all be similar with regard to efficacy and tolerability. Merck's Januvia already inhibits the target by ~80% in vitro, and it's hard to imagine that a meaningfully higher efficacy or weight loss will be observed in Roche's program. Nonetheless, it is possible that off target effects could improve or decrease the efficacy of any particular DPP-4 inhibitor; this is not totally far-fetched, since DPP-4 is a protease, and there is no such thing as we understand it as a completely selective protease

inhibitor. There was no mention of aleglitazar, Roche's PPAR gamma modulator. Last quarter, management stated that there would need to be a "serious heart-to-heart" to figure out the target profile for which this drug would aim. Phase 1 studies of R1511, a glucokinase activator, are ongoing.

- **Seattle Medical—Closing series B financing after raising $35M:** Seattle medical closed its series B financing, oversubscribing the round to $35 million. Three new investors (Canaan Partners, Skyline and Intersouth) were added to the company's two series A investors (Three Arch and Frazier Healthcare).

- **Nektar— Dropping inhaled insulin pursuits on lung cancer worries:** Nektar Therapeutics has terminated the development of next generation insulin (NGI) and abandoned plans to find a new marketing partner for Exubera following reports that Exubera may be associated with lung cancer. As a reminder, Exubera was brought to market by Nektar and Pfizer but was discontinued in October of 2007 after it failed to gain market traction; rights to Exubera were returned to Nektar. Now the companies note that Exubera may have been correlated with lung cancer: of the 4,740 patients who used Exubera in clinical trials, six have developed lung cancer, compared to only one of the 4,292 patients in the placebo group. All patients who developed lung cancer had a prior history of cigarette smoking, and we cannot know for certain whether Exubera played any role in their disease. Although the difference in cancer rates between the two groups is not statistically significant (we calculate a p value of ~0.17 or about a 1/5 chance of being a "fluke"), the data are likely to fuel safety concerns about inhaled insulin and may further thwart the acceptance of inhaled insulin. As we have written before, even if there are no concerns, we believe that *perception* of safety concerns about inhaled insulin would persist until long-term data are available for patients and healthcare providers.

  The news is one of a series of recent events that suggest that the promise of inhaled insulin may never materialize. With Nektar dropping NGI insulin and Exubera, and Lilly/Alkermes and Novo bowing out of the inhaled insulin space earlier this year, MannKind's Technosphere Insulin (TI) is the last man standing among the late-stage inhaled insulin products. The latest news presents another large hurdle for MannKind development of TI; although the association between Exubera and lung cancer is not concrete, safety concerns about pulmonary insulin may ultimately be difficult for MannKind to shake. For now, the company is suspending its partnership discussions until phase 3 data are unblinded. MannKind has argued that even if Exubera were associated with lung cancer (a big if), TI would not necessarily carry the same risk because the two drugs contain different particles. Safety data for TI has been promising thus far: MannKind has completed two year carcinogenicity studies for TI in rats, and according to CEO Alfred Mann, the company has observed no toxicity effects. Studies in tissue culture have shown that unlike Exubera, TI has no effect on the tight junctions between cells in the lung, even at several times the clinical exposure. Approximately 2,600 patients are enrolled in the MannKind phase 3 program, bringing the total number of patients who have been exposed to TI to 3,000. The company has observed a single case of lung cancer in its clinical program, which according to MannKind is not higher than would be expected in the general population. Nonetheless, we believe the onus will be on MannKind to prove to patients, healthcare providers and regulatory agencies that TI is not associated with lung cancer – a challenging position, to be sure.

- **Tolerex— Anti-CD3 drug advances to phase 3:** Tolerx announced on April 9 that it is advancing otelixizumab, its anti-CD3 monoclonal antibody, into phase 3 clinical testing. The phase 3 study is called Durable Response Therapy Evaluation For Early or New Onset Type 1 Diabetes (DEFEND, an excellent name in our view) and will be conducted at multiple clinical centers in Europe and North America. The study will measure the effect of a single course of

otelixizumab on stimulated C-peptide levels, a surrogate measure of beta cell preservation. DEFEND enrollment is expected to begin in mid-2008. Tolerx is partnered with GSK in the development of otelixizumab. Macrogenics's teplizumab is another similar anti-CD3 antibody in development, currently in phase 2/3.

CD3 is a protein complex expressed on all T lymphocytes (T cells) that is required for signaling (CD3 is not actually a receptor, though it is an integral component of a large complex that includes the T cell antigen receptor [TCR], which is the part of the T cell that recognizes foreign material such as pieces of viral or bacterial proteins). By binding to this complex, humanized anti-CD3 antibodies including otelixizumab are thought to block the function of autoreactive T cells, which have been implicated in autoimmune diseases such as type 1 diabetes (basically, no one knows how these antibodies work). In addition to destroying autoreactive T cells immediately, anti-CD3 antibodies are believed to simultaneously create regulatory T cells that continue to keep autoreactive T cells at bay for a prolonged period of time (we don't actually have the technological know-how to prove this right now). How long? Nobody knows for sure, but in a phase 2 clinical trial of 80 new-onset type 1s, six-day treatment with otelixizumab helped to reduce insulin requirements for patients for up to 18 months.

We heard some anecdotal discussion at ATTD that some patients continue to have reduced insulin requirements to this day (almost four years after the original treatment). Some researchers hope that by administering otelixizumab as soon as type 1 diabetes is diagnosed, it may be possible to greatly prolong the so-called "honeymoon period" when some beta-cells are present and actively producing insulin. By preserving beta-cell function, patients may experience improved glycemic control, reduced hypoglycemia, and reduced long-term complications of diabetes. In our view, there may come a time when anti-CD3 antibodies are used in combination with other promising strategies such as antigen-specific agents or even GLP-1 or gastrin for an even greater effect. From speaking to our advisors, as we understand it, if this does work, other immunosuppressive therapies would likely be developed as well—this appears to represent a pretty brute force way to prevent beta-cell destruction, and more targeted therapies are probably possible, though as a starting point it may be quite valuable. We are very eager to watch progress on this front.

- **Abbott—1Q08 very strong internationally, with blood glucose monitoring up 23%:** On April 16 in a call led by CEO Miles White, Abbott Diabetes Care reported 1Q08 worldwide sales of $325 million, up ~14% versus a year ago. Sales outside the US were especially strong, coming in at $189 million, up 23% versus 1Q07 on a reported basis (~11% without positive currency impact). Abbott continues to achieve strong double-digit sales in emerging markets, particularly China, India, and Latin America. Domestically, sales were $136 million, up 4% from last year and flat with 4Q07. The highlight of the call on the diabetes front was the US launch of the Navigator CGM on the week of April 7. In an early market, more resources should lift all boats – we expect Abbott's launch to be positive for industry as a whole. All eyes will be on JDRF in the coming months as the wait for the preliminary data from the first six months of its CGM trial begins. We believe a half point drop in A1c would be a real positive, particularly if significant reductions in hypoglycemia are achieved.

- **J&J—Diabetes Care posts robust international growth:** During its 1Q08 earnings call on April 15, J&J reported that its Diabetes Care franchise (LifeScan, Animas, and JJDI) had global revenues of $615 million for the quarter, up 12% from last year (~6% operationally/with currency impact) and down 4% sequentially from 4Q07 revenue of $643 million. Within J&J's diabetes franchise, while international sales growth was robust, up 21% to $312 million, the US market was tougher, where sales increased 4% to $303 million. While the US is becoming a more competitive

market, J&J certainly remains a frontrunner with its huge base, now annualizing at $2.5 billion, and with JJDI (see below) now driving education, a key to expert diabetes management, in our view.

Animas was again a strong contributor to Diabetes Franchise growth, with its sales up double digits – management said that this was a driver for US growth. We would have liked to hear more specific quantification, since the last two quarters were up 30% and 40% at Animas and we loved hearing the specifics – but double digits for a pump business competing against Medtronic's pump-CGM offering is quite good in our view. That Animas is contributing to pump market expansion is testament to its strong consumer market understanding and very strong relationships with healthcare providers (a big influence to patients) as well as with patients and families themselves. We look forward to the launch of the Animas/Dex Com CGM as we know many Animas users are looking for a CGM pump offering – we also continue to believe that more CGM marketing will be very positive for the market overall.

Overall, we look for J&J's presence in diabetes and obesity to continue to strengthen, particularly with the launch of JJDI (J&J's Diabetes Institute – now open in Silicon Valley and Japan and to open shortly in France and China) and the recent acquisition of Children With Diabetes (CWD). Treating diabetes and metabolic disease has been important to J&J over a long period of time – the company acquired LifeScan for $100 million in 1986, Obtech (a Swedish gastric banding company) for $110 million in 2002, and Animas for $518 million in 2005. Although J&J didn't discuss JJDI and CWD on the call, we believe they will be important to what we think J&J already does best – understanding its customers and their needs.

- **Merck—Taranabant looks like rimonabant in phase 3 trials**: Dr. Ira Gantz presented phase 3 taranabant data in a poster presentation at the 57th Annual Scientific Session of the American College of Cardiology in Chicago, on March 31. The 52-week trial of taranabant randomized approximately 2,000 subjects to placebo, 2 mg, 4 mg, or 6 mg taranabant doses, all with continued diet/exercise (part of the trial). However, early in the trial the study's Data Safety Monitoring Committee recommended re-randomizing patients taking the 6 mg dose to the 2 mg or placebo arm due to a higher incidence of adverse events without a significant difference in efficacy. The efficacy data presented provided nothing new beyond what was in the abstract that was released earlier in the month (and discussed in March DCU). Patients achieved a 2.6 kg weight loss in the placebo arm, a 6.8 kg weight loss in the 2 mg arm, and an 8.1 kg loss in the 4 mg arm (amounting to about 4.0% and 5.5% weight loss for the 2 mg and 4 mg dose, relative to placebo). Approximately 57% of patients in the 2 mg treatment group achieved 5% weight loss, compared to about 27% of patients in the placebo group. Dr. Ganz did not comment on this with respect to the FDA's requirements but we believe these efficacy figures would meet the expectations of FDA guidance. The only other endpoint reaching clinical significance was HDL (13.2 mg/dl rise in 2 mg arm and 14.1 mg/dl rise in 4 mg arm). Changes in fasting plasma glucose and LDL were negligible.

  The poster did shed some more light on taranabant's side effect profile, which is very similar to Sanofi-Aventis's rimonabant. This is not surprising given that taranabant and rimonabant are structurally very similar compounds that are both antagonists of the cannabinoid-1 (CB1) receptor, but it is inconsistent with Merck's previous statements during its Annual Business Briefing on December 11, 2007, and at other venues that taranabant has a much wider therapeutic index than rimonabant. At 52 weeks, the most common adverse events were gastrointestinal in nature and were statistically more common in both the 2 mg and 4 mg arms in comparison to placebo (42% in 2 mg, 47% in 4 mg, 46% in 6 mg, and 29% in placebo). Perhaps more worryingly, psychiatric adverse events occurred in 40% of the 4 mg arm, twice the 20% incidence in the

placebo arm (the 2 mg arm was 28%). Depressive disorders were observed in 8.9% and 10.6% of patients in the 2 mg and 4 mg dose groups, respectively, compared to 6.5% of patients in the placebo arm.

Following the presentation of phase 3 data, Merck announced that it would only study the 2 mg dose of taranabant moving forward. Given the growing interest in combination therapy, we imagine some part of Merck's big interest in taranabant will be related to possible combinations with Januvia/Janumet. Information was not given on any A1c reduction though we assume this wasn't significant, given that fasting glucose did not change substantially. We believe that the commercial prospects of a combination of Januvia/Janumet with taranabant for use in either patients with diabetes or pre-diabetes could be big if major safety issues with the 2 mg dose don't emerge; that said, currently many safety issues surround this class. No doubt Merck will be happy to watch rimonabant's progress closely and let Sanofi-Aventis lead the way.

- **J&J—Adding Children With Diabetes, Inc. to the Franchise: On** March 28, 2008, Children with Diabetes, Inc., announced that it would join the Johnson & Johnson Family of Companies as part of the Diabetes Franchise. We see this as a positive for patients and healthcare providers as CWD will have more resources to expand its incredible presence, which includes the much-trafficked childrenwithdiabetes.com website, the Quilt for Life, and the Friends for Life conferences. We recommend that *anyone* with a child with diabetes and anyone who would like to learn more about diabetes should attend a Friends for Life conference – the community that Jeff Hitchcock and Laura Billetdeaux and their incredible team have created is something stunning, to be sure. We look forward to hearing about more international expansion for CWD in the months and years to come.

- **Pelikan/Eli Lilly—Teaming up on diabetes education initiative:** On April 16, Pelikan Technologies and Eli Lilly announced that they will work together to advance education about good diabetes management and treatment, via insulin therapy, insulin delivery devices and lancing technologies that support self-monitoring of blood glucose. In this "awareness" deal, Pelikan benefits from the Lilly association and Lilly benefits from being linked to a technology that may expand testing in those that are needle (or lancet) phobic. Neither company's role in the educational initiative has been comprehensively outlined and the economics of the deal were not disclosed. We do believe there would be interest in the combined meter/lancing device that continues in the works at Pelikan – the timing on that anticipated FDA filing is now 2009. The goal of an all-in-one product could be incrementally beneficial for some segments, particularly combined with less painful lancing for those seeking the convenience of all-in-one. We look forward to seeing data published for the all-in-one product.

- **Novo Nordisk—NovoLog approved for insulin pumps in children and adolescents:** On March 18, Novo Nordisk announced that the Food and Drug Administration (FDA) approved the use of NovoLog in insulin pumps for pediatric patients (ages of 4 and 18 years). No other insulin analog is currently FDA approved for this use though insulin analogs are all used fairly routinely in pumps. One of the common problems with pediatric medicine is that data is often lacking for children using various therapies because of the small size of the market, leaving healthcare providers to guess about drug doses and safety profiles in children. However, Novo Nordisk certainly seems to have done the legwork in order to get FDA approval of NovoLog for the adolescent population. It funded a study that randomized 300 children in a 2-1 fashion to NovoLog CSII or Humalog CSII. The study, which was published in the February issue of *Diabetes Care*, found comparable changes in A1c and rates of hypoglycemia between the two groups. Based on the data from this study, the authors of the study concluded that NovoLog is effective, safe, and tolerable in pumps for the pediatric patient population.

- **Metabasis—Filling in for the discontinuation of CS-917:** During the Metabasis 4Q07 earnings call on March 17, President and CEO Dr. Paul Laikind provided an update on the development of MB07803, the company's second-generation fructose-1,6-bisphosphatase (FBPase) inhibitor that is currently in phase 2a. This drug may reduce the production of glucose from the liver. Metabasis completed enrollment of a 100-patient, 28-day study of MB07803 and expects to deliver top-line results from the study in 2Q08 (but probably not in time for ADA, we learned at the 28th Annual Cowen Health Care Conference in Boston). Dr. Laikind said that MB07803 was selected based on preclinical studies that indicated it had a more favorable pharmacokinetic profile than the company's first generation FBPase inhibitor.

  As a reminder, the company's first generation FBPase inhibitor (CS-917), which was being developed in partnership with Daiichi Sankyo, was dropped after it failed to significantly reduce A1c levels in a three-month phase 2b clinical trial. Dr. Laikind has previously asserted that the results for CS-917 were a failure of trial design, including an unexpectedly low baseline A1c of 7.6%. Metabasis showed during the 3Q07 earnings call that a subgroup analysis conducted by Daiichi Sankyo provided evidence of efficacy. Although Metabasis now holds all rights to CS917 following the termination of its partnership with Daiichi Sankyo, the company does not plan to move the molecule forward given the improved profile of MB07803. Dr. Laikind said that MB07803 had other benefits over CS-917 including once-daily dosing, improved bioavailability, improved potency, reduced metabolism, and reduced drug variability, and he said that phase 1 data supported these assertions. We look forward to seeing the results of the phase 2a study, but we have reservations about the efficacy of this molecule in monotherapy (even accepting the improved profile of MB07803 and the trial design issues for CS-917). Regarding combination therapy, Metabasis is planning to conduct a drug interaction study for MB07803 with metformin.

  Dr. Laikind said that Metabasis is continuing to develop new preclinical drug candidates, including a glucagon antagonist and an AMPK activator. Metabasis's AMPK program is being conducted in collaboration with Merck. At the end of 2007, Metabasis had $42 million in cash and cash equivalents and management forecasted operating expenses for 2008 in the range of $51 to $56 million. Management said that new cash flows from new corporate collaborations and other sources of funding were likely in 2008 – whew! Excluding these new cash flows, management said that cash usage in 2008 would fall between $40 and $45 million, raising the question of funding needs.

- **Sirtris—First patent issued covering NCEs:** On March 19, the US Patent Office (USPTO) granted Sirtris its first patent covering a broad class of New Chemical Entities (NCEs) that activate SIRT1. The patent covers approximately 800 of the company's preclinical NCEs including one that Sirtris hopes to bring to the clinic later in 2008. While the issuance of this patent does strengthen the company's intellectual property portfolio, the patent does not prevent other companies from developing other novel SIRT1 activators for diabetes or other diseases. Sirtris has submitted approximately 180 patents to the USPTO, including some broad mechanism-of-action patents. The company looks for its mechanism-of-action patents that describe the activation of sirtuins for the treatment of diabetes, cancer, cardiovascular disease, multiple sclerosis (MS), and MELAS to issue in the next 12 to 18 months.

- **Insulet—Strong 30% sequential increase in customer base in 4Q07:** During the Insulet 4Q07 earnings call on March 18 led by CEO Duane DeSisto, management reported impressive fourth quarter user growth with 4,150 users at last count, up 30% from last quarter and tripling since 2006. Revenues came in at $4.4 million, up 15% sequentially and 166% year over year. Net losses were $15.7 million, up 15% sequentially from $13.6 million ($0.52 per share) last quarter and up 44% from $10.9 million ($27 per share) in 4Q06. Management stated that they expect to

achieve revenues of $40 to $45 million in 2008 and positive gross margins no later than 4Q08. Full year revenues came in at $13.4 million, up 260% from 2006. Cash and cash equivalents as of December 31, 2007, were reported at $95 million.. Spending came in higher than planned and ROI will be key to assess exiting 2008.

Insulet is rapidly expanding its sales force and manufacturing capacity. Current manufacturing capacity for the OmniPod is 75,000 pods per month. Management expects to exceed the 200,000 pods per month goal they initially set for the end of 2008. They predicted reaching output of 400,000 pods per month by the first half of 2009 – six months before previous guidance. This is of course dependent on having the Flextronics manufacturing facility in China fully operational, which management expects to happen in 4Q08. We believe that 200,000 pods per month would be associated with about 15,000 customers, so this is a significant step up. Insulet continues to accelerate OmniPod rollout, hiring 23 additional territory managers since end-of-year 2007, bringing the total number to 40. Insulet now has access to 146 million covered lives, up slightly from 3Q07.

Management also said that Insulet plans to announce the first non-diabetes drug delivery application of the OmniPod by the end of 2008. The company has two candidates going through testing and expects to have an agreement reached this year. No further details about the compounds being delivered were provided. Management also highlighted its recently signed partnerships with DexCom and Abbott Diabetes Care related to CGM integration with the OmniPod. A separate, recently amended deal with Abbott positioned Abbott's Freestyle meters as the exclusive meter available in the OmniPod, presumably a positive for Insulet on the economic front.

- **Oramed—Oral insulin moving to phase 2a:** On March 18, Oramed Pharmaceuticals, an Israeli-based company, announced that it has been granted approval by the Institutional Review Board (IRB) committee of Hadassah Medical Center in Jerusalem to conduct a phase 2a study of oral insulin in people with type 2 diabetes. The phase 2a study is targeted to begin in 2Q08 and will last several months. While we applaud any efforts to reduce the burden of insulin initiation, we recognize that the development of orally ingestible insulin capsule is difficult, and there is relatively little research overall in this arena. We look forward to learning more about the pharmacokinetic and pharmacodynamic properties of Oramed's oral insulin when the study results are released but we are skeptical about any real progress happening in this domain.

*—by Kaku Armah, Kelly Close, and Mark Yarchoan*

## 4. DCU Dialogue with Dr. David Orloff

*Dr. David Orloff spent 11 years at the U.S. Food and Drug Administration, the last five as the director of the division of metabolism and endocrinology products, which is responsible for review and approval of drugs to treat, among others, diabetes, lipid disorders, and obesity. In 2006, he joined MedPace Inc., a contract research organization based in Cincinnati with a therapeutic focus in metabolic and cardiovascular disease. He attended Harvard College and the New York University School of Medicine, graduating in 1984. After a basic science and clinical endocrine fellowship at NIH, he joined the FDA in 1994. In a conversation with Kelly Close and Mark Yarchoan, Dr. Orloff discussed the FDA's rising standards for drug safety, the shifting definitions of a diabetes drug, the state of inhaled insulin, and more.*

Kelly Close: Generally, what is your view of type 2 diabetes in the US today, and how will drug development affect this over the next few years?

Dr. Orloff: I believe it continues to be a very exciting time in type 2 diabetes research, with continued advancement of new molecules to address new targets. Clearly, combination therapy has become the rule rather than the exception in the increasingly sophisticated medical management of type 2 diabetes, so that at this point there is universal recognition that there is no one drug solution to the problem. Companies are now more willing, and I believe FDA is more attuned to, the investigation of potential new diabetes drugs that may not be as dramatically effective at lowering A1c as was envisioned as desirable and necessary in the past. The concept of using several drugs, each with only modest effects, but safe and well tolerated, which added together effect robust clinical improvements is increasingly attractive, and I trust commercially viable. Obviously this raises issues around drug-drug interactions as well as complexity of self-care, but these are all issues with which the medical community is quite familiar and I think generally comfortable. Overall, I'm optimistic for the future of diabetes therapeutics, notwithstanding regulatory hurdles, related particularly to safety concerns.

Kelly: As far as drug development goes, A1c is still the gold standard in terms of primary outcomes, but we've been hearing more and more about other measures. What benefit might companies get from running long-term outcome trials?

Dr. Orloff: I think it is appropriate that A1c should remain the basic standard for drug approval. This is the position that FDA has re-emphasized in their recent draft guidance for the clinical development of drugs for diabetes. There is a time and a place for everything. That is, there needn't and shouldn't be an across the board requirement for demonstration of reduced morbidity and mortality related to the complications of diabetes. Glucose lowering is a valid surrogate for clinical benefit at least related to the microvascular diseases of diabetes. That said, I am supportive of the FDA's position that in the event that a new drug is associated with a worrisome safety "signal", most particularly related to cardiovascular risk, then outcome studies may well be necessary for approval. That would be the case whether they were considering a hypertension drug, a diabetes drug, a lipid drug, all of which are taken specifically to reduce cardiovascular risk, so we all need to be pretty darned sure the surrogate effects are telling the important part of the story. In truth, I don't believe that this represents any sort of a change in FDA's longstanding approach. I don't think it represents a new hurdle for pharmaceutical companies. However, we all recognize that the FDA is more overtly focused on drug safety than they ever have been before. There has long been a very high standard for drug safety, but in terms of trials that need to be done to "prove" safety, or better said, to rule out risk – that is where the bar has been raised. And, of course, companies that do conduct endpoint trials – that constitutes an advantage for them in the marketplace. We're all trying to practice evidence-based medicine; what better evidence could there be than hard outcomes?

Kelly: What stage new chemical entities do you see the proposed new FDA guidelines applying to? All NCE's pre-Phase 3 or all NCE's pre-NDA? Is there any possibility you could see that those new guidelines could be applied to drugs that already have been approved, to which there are follow on drugs – like Byetta and LAR, for example?

Dr. Orloff: I think it applies to all new drugs for diabetes. If you mean retro-actively requiring hard outcomes studies, this would be difficult to enforce, but there is every reason to believe that companies could be "convinced" to do what was necessary to characterize the risk versus benefit of an already approved drug.

**Glycemic Variability: Moving toward Another Accepted Target?**

Kelly: Some companies are arguing that they may not show an A1c reduction, but they are reducing glycemic variability. Will this become an accepted surrogate, do you think?

Dr. Orloff: For other measures to become accepted surrogates, their surrogacy has to be defined. In other words, clinical studies are necessary to show that less glycemic variability confers some kind of unique benefit, despite the fact that the drug with this effect might not be a big A1c lowering agent. In the hypothetical, if you had a drug that you could add to a big A1c lowering drug, and the overall glycemic variability was reduced, causing less weight gain and hypoglycemia, conceivably that could be viewed as a useful adjunct to HbA1c lowering agents acting primarily on fasting glucose control.

Kelly: What sort of a trial could show that less glycemic variability confers some sort of benefit?

Dr. Orloff: I don't' know what the right study is. To some extent you could argue that Byetta and certainly Symlin reduce glycemic variability. [But] I get the sense from the guidance that there is a negative attitude toward drugs that don't lower glucose – drugs like Symlin. Maybe the suggestion ought to be that we need to think more broadly about what a type 2 diabetes drug really is. According to the historical regulatory approach, a diabetes drug is a drug that directly lowers glucose. Up to the mid-90s in the US, the only available approved drugs were insulin and sulfonylurea. We've become more clever about glucose disposal recently, but unless we reinvent the human being, glucose disposal will always require insulin or an insulin receptor agonist. All diabetes drugs involve the pathway of insulin, but we have multiple ways with which and multiple places at which to modulate that system. For example, you can make peripheral tissues more sensitive; manipulate the rate of hepatic glucose production, stimulate the beta-cell to secrete insulin, all with multiple different pharmacologic approaches. In the ideal world, there would be a different definition of a diabetes drug than the one we currently have. But first we need an agreement about what improvements or changes in physiology and energy metabolism are going to benefit people with type 2 diabetes. Targeting those changes, arguably, regardless of whether they are directed at the insulin system, makes a diabetes drug. What I've just stated is the fundamental hurdle that the obesity community has grappled with. The obesity researchers have long argued that if you give an obesity drug to a person with type 2 diabetes, and they lose weight, and their diabetes improves, then it's a diabetes drug. That would seem self-evident, but it's complicated from a regulatory standpoint.

**How to Define Pre-Diabetes and Diabetes Itself**

Kelly: What would companies have to see for a pre-diabetes indication?

Dr. Orloff: Some have argued that the way to get approval for a drug for pre-diabetes is to change the definition of diabetes. It's pretty evident that the historical definition of diabetes – sugar in the urine, and everything that came along with that like wasting, starvation, ketoacidosis – is no longer a particularly relevant disease definition. The goal used to be simply to keep sugar out of the urine. If there wasn't sugar in the urine, we said that glucose was well controlled. Now we have A1c goals, post-prandial goals, fasting goals, etc. and the glycemic criterion for diabetes is such that you have to be well above it to spill significant amounts of glucose in the urine. The rationale for treating pre-diabetes would be of course to stave off diabetes, and potentially to "normalize" glucose metabolism to reduce even the relatively low risk of complications related to chronic mild hyperglycemia.

Kelly: On that note, are the ADA's glucose goals too lenient?

Dr. Orloff: I don't know; I'm not the person to answer that one. As you know, the ADA definitions are based upon the relationship between glucose and microvascular disease risk. The curve flattens out quite a bit at about 130 mg/dL, but there is still an elevated risk relative to true normoglycemic individuals of microvascular complications such as retinopathy below 126 mg/dL. To shorten a long story, it's time to think of concepts beyond diabetes mellitus, or

sweet urine. That's an archaic term, because it doesn't describe the syndrome we're treating. Somebody needs to change the definition such that we can begin to intervene at earlier stages.

Mark: Why do you think there's so much resistance about changing the definition of diabetes?

Dr. Orloff: Let's just accept that we have a definition of diabetes that's based on glucose. When you treat diabetes, you can say, "Okay, I know based on epidemiology this person's probability of developing stroke, cardiovascular disease, retinopathy, neuropathy, etc. is x. I have a tangible measure." Conceptually, it's easy to say that for reducing the risk of those outcomes, I'm willing as a society to pay dollars, and I'm willing as a patient to accept certain side effects and risks of the drug itself. Since things I'm trying to prevent are tangible, there's a value judgment that can be made. Things get more difficult when you practice the prevention of diabetes. You suddenly bring in a new list of complicated calculations. What's the chance of this guy actually getting diabetes? They don't have the diabetes yet. Indeed, it may be a long way off, if it ever occurs. As a population, people with prediabetes have a much lower risk of complications of diabetes, because they have to first develop diabetes. Therefore, you have to raise the bar on what's needed with regards to the safety of the drug. All of these factors are theoretically calculable, but by definition, since the safety of the drug doesn't change whether you're treating diabetes or prediabetes, the risk vs. benefit becomes less favorable.

Kelly: Were you surprised by the draft guidance? It seemed like it opened the door a little bit toward prediabetes. This was very positive from our view. What was your reaction?

Dr. Orloff: I wasn't very surprised by the draft guidance. I'm not sure what they're saying is different than the principles that I've laid out. The document's 20 lines about prevention of diabetes simply means that they're entertaining thoughts about it while recognizing that the safety bar will be very high.

Kelly: What do you think are the most important trials that companies in diabetes could do?

Dr. Orloff: I don't have a very exciting answer here. I think that there's a well-marked path to approval of a diabetes drug. It's about lowering A1c alone or in combination with other agents. I don't see an immediate necessity or importance to going beyond that. I think there's a risk of having unacceptable side effects to achieve a large A1c reduction. One of the fundamental concepts behind combination therapy is to enable the use of lower doses of multiple drugs.

**Inhaled Insulin's Uncertain Future**

Mark: To switch gears, we'd love to talk to you about inhaled insulin – is there still a chance? Does MannKind have to prove that it does not cause lung cancer?

Dr. Orloff: Broadly speaking, I think that it is becoming evident that what some might have thought was a promising area of therapy is not anywhere close to delivering what was anticipated. What was anticipated with inhaled insulin was convenience, tolerability, and glycemic control. The convenience part took a big hit with the restrictions on Exubera and pulmonary screening. I think it's fair to say that inhaled insulin might be a really great substitute for some to injected insulin, but I think it's self-evident that subcutaneous insulin is going to provide a wider range of dosing on a day-by-day basis. I just think that for rapid-acting insulin, it seems highly unlikely that the hurdles are going to get anything but higher. Each time you think you clear one, there's another one that comes along. The other thing that we keep hearing about is long-acting inhaled insulin. That in theory brings back into play convenience. If both inhaled basal and rapid-acting inhaled insulin are available, it will be possible to completely eliminate the need for injections. Again, I think it's intriguing, but the deck is being stacked against inhaled insulin. At this point, there is inadequate information to address the question of lung cancer

risk with inhaled insulin. Personally, I question the plausibility of insulin as a growth factor in the pulmonary epithelium, given the well-documented benign histological effects of chronic inhalation of insulin in experimental animals and the absence of irreversible functional effects in man that would suggest tissue changes.

Kelly: We'd also like your thoughts about clinical trials that are designed to report time in euglycemia. This has to be done with CGM, I think. What do you think about this sort of reporting in clinical trials? Is time in euglycemia a valuable secondary measure?

Dr. Orloff: Conceptually, time in euglycemia a very attractive idea. From a therapeutic standpoint, it shows that we're refining our view of the daily cycle of glycemic control. We're integrating time in the abnormal and time in the normal range. In theory, that's what A1c does, but A1c is more crude because it doesn't enable you to discriminate when you had the spike that drove your average up. I believe that time in euglycemia is potentially as good a marker as A1c with regards to risk, but there is a lot of work to be done to refine the approach to assessment and then to correlate with HbA1c and risk.

**The Pipeline for Obesity Drugs**

Kelly: Regarding obesity drugs, is there anything in the pipeline that you're particularly intrigued by?

Dr. Orloff: I would say that I'm particularly intrigued by peripherally-acting obesity treatments, as opposed to centrally-acting treatments. Centrally-acting drugs have historically been the most effective targets from a medical perspective. If it's possible to get away from appetite suppressants, it would serve the field very well. I think that it's very significant that there are heightened concerns over the mood effects of all kinds of drugs, particularly drugs that target the CB1 axis. Given what's going on there, there would seemingly be a much easier path for obesity drugs with a peripheral mode of action.

Mark: On the diabetes side, what are you most intrigued by?

Dr. Orloff: I don't have a specific comment beyond what I've already said. Let's just say that the hope for patients with type 2 diabetes is a broader swath of peripherally-acting agents that are not associated with hypoglycemia. That's pretty obvious. In type 1 diabetes, the goal has been to develop formulations of insulin that have kinetic and dynamic profiles that enable fine adjustments in insulin activity. And of course, we're getting closer and closer to the closed loop. With CGM and insulins with very consistent time activity profiles, patients with type 1 diabetes have much better tools than ever before. It sounds promotional, but there's a lot of hope there. It's not the same as a beta-cell, but if you work carefully today, you can do quite well.

Kelly: The last question: Do you miss your job at the FDA?

Dr. Orloff: I value the experience that I got at the FDA. I certainly value the many friends and colleagues that I worked with all that time, and I admire and respect their continued work in diabetes and metabolism. But for myself, I find that I'm very satisfied with the work that I can do now to help directly in drug development in these areas, from study design and planning through clinical trial implementation.

Kelly: We can't thank you enough for all you do for patients and for families and for providers in the US and globally Dr. Orloff. So much appreciation for your time with us.

## 5. Conference Pearls: American College of Cardiology (ACC)

*The 57th Annual Scientific Session of the American College of Cardiology took place in Chicago and included the release of results from several key trials in diabetes and obesity. Before the start of official conference activities, we attended two pre-conference symposia addressing cardiovascular risk reduction and the management of diabetes. Both sessions were very well attended: one theme that emerged was the increasingly blurred line between endocrinology and cardiology.*

*Some of the notable trial results shown on days two and three include Dr. Steven Nissen's presentation of the results from the PERISCOPE and STRADIVARIUS trials, as well as a poster presentation of the full phase 3 data on Merck's CB-1 receptor antagonist taranabant (see Merck company watch on page 11 for details). The PERISCOPE results showed that pioglitazone was superior to glimepiride in preventing carotid intimal-media thickness (CIMT) increase in patients with type 2 diabetes – a surrogate measure of atherosclerosis. The STRADIVARIUS results were more mixed, with rimonabant failing to show a statistically significant effect on percent atheroma volume (PAV), the surrogate measure of coronary artery disease measured in this trial. Below are our highlights from the meeting.*

- **UK's NICE endorsed the use of Sanofi-Aventis's rimonabant:** On March 26, the UK's National Institute for Health and Clinical Excellence (NICE) issued its Final Appraisal Determination in favor of the use of rimonabant in patients who have not responded to or cannot take other anti-obesity drugs. The decision comes as somewhat of a turnaround from the organization's draft technology appraisal issued in December of 2007. In that draft guidance, NICE called for more information comparing the efficacy and safety of rimonabant to lifestyle modification and other obesity drugs, including orlistat (Roche's Xenical and GSK's Alli) and sibutramine (Abbott's Meridia). We were surprised to see this decision since NICE generally errs on the side of caution when it comes to new or expensive therapies.

- **Dr. Steve Nissen of the Cleveland Clinic addressed a crowd of over 1,000 people when he presented preliminary data from the PERISCOPE trial.** The Effect of Pioglitazone versus Glimepiride on Progression of Coronary Atherosclerosis in Patients with Type 2 Diabetes trial was a double blind randomized controlled study between a TZD - pioglitazone (Actos, Takeda) - and an SFU - glimepiride (Amaryl, Sanofi-Aventis) - with an endpoint of carotid intima-media thickness (CIMT) as measured by intravascular ultrasound (IVUS). The preliminary data showed an absence of progression of plaque buildup with pioglitazone (-0.16%) in comparison to significant buildup with glimepiride (+0.73%). Lipid parameters were also more favorable for pioglitazone (not surprising, given previous data on this front). In what was perhaps a jab towards Avandia, Dr. Nissen noted that it is important to evaluate each TZD independently, and the beneficial effects observed with pioglitazone could not be applied to other drugs in this class.

- **Dr. Nissen also presented the results from the Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant (STRADIVARIUS) trial, designed to examine the effect of rimonabant on progression of coronary artery disease in patients with abdominal obesity and pre-existing coronary disease**. Overall, results were a mixed bag: administration of rimonabant, 20 mg daily, for 18 months did not significantly affect PAV (percent atheroma volume), the study's final endpoint, but did have a favorable effect on the secondary endpoint, TAV (total atheroma volume). In the rimonabant vs. placebo groups, PAV increased 0.25 percent vs. 0.51 percent, respectively, and TAV decreased 2.2 mm vs. an increase of 0.88 mm. Among the subset of patients enrolled in the study with diabetes (n=225), mean A1c in the rimonabant group decreased by 0.13%, while the A1c in the placebo group rose by 0.42%, beginning from a low baseline of 6.6%. This was technically significant although we don't think it was especially notable. Results from these trials were simultaneously published in *JAMA* on April 2.

- **An oft-asked question discussed at this conference was: "Do all diabetics need a statin?"** And the answer, by Drs. Steven Haffner of the University of Texas Health Science Center and Dr. Jack Leahy of the University of Vermont was: "*No . . . but almost all do*."

- **Dr. Louis Aronne, Director of the Comprehensive Weight Control Program at New York Presbyterian Hospital/Weill Cornell Medical Center, noted that most intensive insulin regimens result in increased weight gain**. He suggested that the potential weight gain and obesity incurred in the intensive insulin arm of the ACCORD trial may be shown to contribute in part to the excess mortality. He then made a case for the use of exenatide (Byetta) in conjunction with weight-gain inducing anti-diabetic agents in order to maintain an overall weight-neutral strategy. Furthermore, he stressed the importance of the exenatide-metformin combination data that suggest meaningful, long-lasting weight loss in patients with metabolic syndrome. In discussing CB1 inverse agonists, Dr. Aronne commented that the adverse event profile that prevented US marketing of rimonabant was likely dose- and labeling-related, and he felt that the data for rimonabant as a treatment for obesity were so compelling that FDA approval of lower dose forms with a restricted label similar to that in Europe would make the drug available in the future.

- **Dr. Jack Leahy, Chief of the Division of Endocrinology, Diabetes and Metabolism at the University of Vermont, spoke about the benefits of GLP-1 therapy in heart failure patients.** He mentioned slowed gastric motility, early satiety, and potentially improved cardiovascular dynamics based on preliminary results from the use of exenatide in this patient population. In a separate symposium on cardiovascular risk reduction, Dr. William Cefalu, Chief of the Division of Nutrition and Chronic Diseases at Louisiana State University, also spoke enthusiastically about the use of Byetta because it addresses postprandial glucose excursions, and therefore more closely mimics the physiological response to a meal.

- **Dr. Richard Nesto, Chairman of the Department of Cardiovascular Medicine at the Lahey Clinic in Burlington, Massachusetts, explained that the evidence in support of utilizing glucose-insulin-potassium (GIK) cocktails in acute myocardial infarction is a "mishmash at best."** Then he highlighted the INTENsive study of Insulin Therapy And Size of Infarct Visual Endpoint, which began enrollment last month. This 60-site, 600-patient study is intended to randomize patients with acute myocardial infarction to an intensive insulin therapy arm (goal glucose 90-130 mg/dl) or a standard care arm (goal glucose <180 mg/dl) with a primary endpoint of myocardial infarction size as documented on contract echocardiography. We will be writing more about this trial in the coming weeks.

- **In his talk, Dr. Nesto also provided a striking obesity statistic**: In the US, nearly one in *three* children reaches a BMI greater than 35 by adolescence. As a reminder, in adults, a BMI of 25 or above signals overweight and a BMI of 30 or above signals obesity.

- **Virtually all the presenters agreed that there is significant inconsistency in the AHA/ACC guidelines surrounding cardiovascular imaging in diabetes patients and patients with heart failure.** A panel convened to discuss cardiovascular imaging guidelines and other related issues came to the consensus that further study over the next decade would redefine the application of imaging technologies in diabetes patients to diagnose and monitor cardiac dysfunction. While there are no commercial applications evident immediately, the future possibility of utilizing echocardiography, CT, or MRI to serially screen diabetes patients for cardiovascular complications could represent a sizable commercial opportunity.

- **Dr. Burton Sobel, Professor of Medicine and Director of the Cardiovascular Research Institute at the University of Vermont, called for increased attention to**

**pre-diabetes and more aggressive management of pre-diabetes** in order to improve the long-term cardiovascular outcomes of diabetes. Dr. Sobel also made the argument that we need drugs that target PAI-1, a factor that inhibits the degradation of clots and is implicated in the pro-coagulant state in diabetes. One additional application of PAI-1 in the drug development marketplace may also be its use as a marker for drug efficacy, and Dr. Sobel noted that the thiazolidinediones (TZDs) reduce PAI-1 activity.

- **Dr. Patrick Boyle, Professor of Medicine at the University of Mexico, spoke enthusiastically about the use of TZDs in pre-diabetes.** He noted that the previous DREAM trial showed almost a 60% reduction in onset of type 2 diabetes and he suggested that a study next year may show a reduction of almost 80% of new onset diabetes for pioglitazone in combination with lifestyle modification. Although TZDs do appear to be very successful at slowing the progression of diabetes, we believe that the drugs are unlikely to be approved for pre-diabetes given the increasing scrutiny of the side effects of the TZDs.

*—by Jenny Jin, Arjun Venkatesh, and Mark Yarchoan*

## 6. In the News: Diabetes Program Gets Lift from United Healthcare

Managing diabetes requires making the right connections – patients with their clinicians, and clinicians with their patients and among each other. Diabetes is too complex to allow anyone to operate in a vacuum.

But that often happens in our fragmented health care system, even at clinics with top-shelf primary care physicians, specialists, administrators, lab technicians, and educators. What's missing in these settings? "The glue that brings them altogether," says Jan Pearson, a senior consultant at the International Diabetes Center at Park Nicollet in Minneapolis, Minn.

Integrating care is a central theme at IDC, but this highly regarded clinic and research center also wants to spread its therapeutic gospel. Six years ago, it took the unusual step of effectively becoming a consultant to other health care organizations. IDC took its best practices and bundled them as a program, calling it Diabetes Connections. The goal is to improve care by focusing on professional education, team building, and customized therapies; the program has been implemented in 30 health care organizations, ranging from large integrated systems to small independent practices to academic centers.

"We come in and engage the entire organization," Pearson says. "It's about building relationships within the organization and between the organization and the community."

IDC now has a chance to raise its profile even higher. Last month, United Healthcare, an insurer, announced that it would pay IDC to implement Diabetes Connections at four pilot sites (the Cleveland Clinic, the Wheaton Franciscan Medical Group in Wisconsin, and the Watson Clinic in Florida. The fourth site has not been identified). The program itself takes 15 to 18 months to install.

Besides the obvious – improving care – Diabetes Connections will hopefully lead to two concrete outcomes for a clinic: certification as an education program by the American Diabetes Association, and certification for the Diabetes Physician Recognition Program, developed by the National Committee for Quality Assurance (NCQA) and the ADA. Both designations are useful for reimbursement, including pay-for-performance measures that are being adopted by some payers.

United Healthcare's support of the program is unusual on several fronts. Insurers are typically not eager to increase their upfront costs on training and education. Those efforts may improve the long-term health of individuals with diabetes, but for insurers, those financial benefits are not quickly realized. In this case,

United Healthcare is not distinguishing between its own patients and those covered by competing insurers. All patients at the four pilot sites can participate.

"It's unusual, but we hope it's a trend," says Dr. Richard Bergenstal, executive director of IDC.

United Healthcare covers more than 750,000 people with diabetes, and contracts with over 500,000 doctors, so it has a clear financial incentive to see diabetic outcomes improve: fewer diabetic complications mean fewer expensive treatments and interventions. The company believes that Diabetes Connections can be a catalyst for improving outcomes. "We need transformational change in medicine," says Dr. Sam Ho, executive vice president and chief medical officer of United Healthcare. "We want to help doctors be the agents of change."

Diabetes Connections includes three different steps:

- *Organizational assessment* that helps an organization obtain a clearer picture of its diabetes care and education, that creates clear goals, and that develops a plan for implementation.
- *Site Training*
    - *Staged Diabetes Management™ implementation* that customizes and standardizes an organization's therapeutic approach to diabetes, emphasizing a team approach to patient care, actively engaging patients in managing their disease, and documenting outcomes.
    - *The BASICS patient education curriculum* that includes tools to teach people with diabetes how to set goals and stay motivated.
- *Follow-up phone calls, site visits and data collection to track, document and celebrate improved outcomes.*

That framework is not radically different from that used by other health care organizations around the country, but IDC believes its initial consensus building – making sure that all of the "stakeholders" have embraced the same goals, have open lines of communications, and are indeed "connected" – is central to the program's success.

"You'd be surprised by the lack of communication," Dr. Bergenstal says.

United Healthcare's experience bears watching. Most insurers would just as soon not have customers with diabetes, because poorly controlled diabetes can be a huge financial burden. But if Diabetes Connections proves to be a relatively low-cost way to improve outcomes, it could change payers' perception of the disease while having significant national implications.

Either way, United Healthcare deserves credit for taking on the challenge. Or as Dr. Bergenstal says, "They're not afraid to the say word 'diabetes.'"

*—by James S. Hirsch and Kelly L. Close*

## 7. Literature Review: Fat-Centered JAMA View of Diabetes in the Spotlight

*In the March 15 issue of* The Journal of the American Medical Association*, Dr. Roger Unger lays out evidence supporting a fat-centered view of type 2 diabetes in an article entitled "Reinventing Type 2 Diabetes." From this perspective, type 2 diabetes is primarily the result of abnormal fat distribution secondary to obesity. Abnormal fat accumulation can lead to insulin resistance in muscle and liver, as well as loss of beta cells due to "lipotoxicity." The clinical implications of this view are significant because it suggests that hyperglycemia itself is more an adaptation to abnormal fat accumulation than the primary disease. Dr. Unger suggests that treatments that lower plasma glucose while increasing*

*body weight (e.g. SFUs, insulin) may amplify some of the negative effects of diabetes. In contrast, therapies that lower body weight (or at least keep it constant) should lead to improved long-term outcomes. This viewpoint provides a strong rationale for treatments such as incretin mimetics that are weight neutral or, in the case of GLP-1 mimetics, cause weight loss. The use of TZDs may also be supported by the fat-centric view of diabetes – although they cause some weight gain, they decrease abnormal fat accumulation and "lipotoxicity." In our view, this article is one of many signs that the diabetes community is beginning to move away from viewing type 2 diabetes as simply a disease of glucose homeostasis, and is instead beginning to view type 2 diabetes as a complex disease driven by abnormal fat accumulation, oxidative stress, inflammation, beta-cell failure, increased gluconeogenesis, and mitochondrial dysfunction. As this view continues to take hold, we expect that the use of sulfonylureas and insulin will decrease in type 2 diabetes, and the use of weight loss therapies (including bariatric surgery) and incretins will increase.*

- **Conventionally, type 2 diabetes is thought of as a primary disease of glucose homeostasis caused by a combination of insulin resistance and beta cell failure.** Insulin resistance is believed to result from obesity through a poorly understood mechanism. Beta cells, unable to generate sufficient quantities of insulin to overcome insulin resistance, eventually fail, leading to a precipitous decline in insulin production. These two abnormalities combine to cause hyperglycemia, which is thought to cause most (if not all) of the long-term consequences of diabetes, including both microvascular and macrovascular disease.

- **Dr. Unger argues that the primary defect in type 2 diabetes may be the manner in which the body stores fat.** When fat cells (adipocytes) are overloaded with fat, additional fat stores form in other tissues. This so-called "ectopic" fat may be the primary cause of type 2 diabetes.

- **Ectopic deposition of fat in muscle and liver may induce insulin resistance.** Fat accumulation in muscle can block expression of the insulin-induced glucose transporter (GLUT-4) on the cell surface, thus preventing muscle cells from taking up glucose in response to insulin. Similar accumulations of fat in the liver prevent insulin-stimulated storage of glucose as glycogen, and block insulin-mediated suppression of gluconeogenesis (glucose synthesis). These actions in both muscle and liver can produce insulin resistance and lead to hyperglycemia.

- **Ectopic accumulation of fat in the pancreas may cause beta cell failure, exacerbating glucose abnormalities induced by insulin resistance.** Fat accumulation in the pancreas appears to be toxic to beta cells, causing beta cell loss, a critical step in type 2 diabetes progression.

- **This fat centered (lipocentric) view of type 2 diabetes suggests that, in many patients, the cycle leading to diabetes begins with the onset of obesity.** The path to obesity begins with a surplus intake of calories mixed with decreased caloric expenditure. Surplus caloric intake leads to increased insulin production (hyperinsulinemia), and increased production of fats (lipogenesis) through the action of a protein called SREBP-1c. Increased fat production causes obesity following the accumulation of fat in adipocytes. Adipocytes are eventually overwhelmed and fat deposits in other tissues, producing insulin resistance and beta cell failure. Insulin resistance and beta cell failure then induce the clinically observed consequence of hyperglycemia.

- **To review, the lipocentric mechanism proposed by Dr. Unger is as follows:** (1) caloric surplus → (2) hyperinsulinemia → (3) increased expression of the lipogenic transcription factor SREBP-1c → (4) increased lipogenesis → (5) increased adiposity → (6) ectopic lipid deposition → (7) insulin resistance + beta cell lipotoxicity → (8) hyperglycemia.

- **Hyperglycemia may be viewed as an "adaptation" to abnormal fat deposition; as a result, therapies targeted solely at lowering hyperglycemia may be unable to reverse the destructive effects of diabetes.** In particular, therapies that provide additional insulin (for example, through increasing insulin secretion or through the direct administration of insulin analogs) may worsen obesity and increase the risk of some complications of diabetes. This seems logical if for no other reason than we know patients gain weight taking insulin; however, the glycemic consequences of not taking insulin may be much worse – this assumes there are good alternatives to taking insulin that reduce A1c as much. Dr. Unger believes that evidence for this view may be buried in the ACCORD trial, although we believe it is important to wait for the publication of the full trial results before jumping to such conclusions.

- **Treating hyperglycemia is extremely important, but, when possible, should be done through therapies that decrease body weight.** Dr. Unger advocates using treatments like insulin and sulfonylureas only as a last resort. Treatment for type 2 diabetes should focus on eliminating the cause underlying the disease, namely, excess accumulation of fat. This view would favor the use of medications like GLP-1 analogs (weight reducing), DPP-4 inhibitors (weight neutral), and metformin (weight neutral) over other therapeutic options, and suggests that long-term outcomes may be substantially better using these alternatives. In addition, Dr. Unger's view strongly supports diet and exercise modification, as well as surgical weight loss treatments. Dr. Unger points to the 73% diabetes remission rate observed following gastric bypass as reported by Dixon and colleagues in the January 23 issue of *JAMA* as an example of the effectiveness of targeting weight as a treatment for type 2 diabetes (see our January 23 Closer Look for details about this study). He does not discuss the side effects of bariatric surgery. Due to the strong link between hyperglycemia and microvascular disease, we believe that hyperglycemia is likely to remain a focus of type 2 diabetes treatment, even if a fat-centered view of type 2 diabetes takes hold.

- **What about the TZDs (Actos/Avandia)?** Dr. Unger does not explicitly discuss the TZD class, and we believe the implications for the TZD class are not immediately clear. Like insulin and the sulfonylureas, the TZDs do cause weight gain; unlike these therapies, however, they also reduce free fatty acids and may prevent ectopic (abnormal) lipid deposition. TZDs mostly increase fat storage in subcutaneous adipose tissue (large fat pads in the hips and other areas), but not in visceral fat (around the intestinal organs, where it is believed to be more detrimental). Therefore, in spite of increasing weight, the TZDs may be effective at treating type 2 diabetes even if Dr. Unger's fat-centered view of the disease is correct. On the other hand, we also believe there is growing patient resistance to therapies that cause weight gain, which would include the TZD class. Furthermore, TZDs if the lipocentric view of diabetes is further adapted, some may begin to question why the TZDs are not associated with the drastic change in CVD outcomes that would be expected from reducing ectopic lipid deposition.

*—by Michael Dougan and Mark Yarchoan*

## 8. Conference Preview: AACE 17th Annual Meeting

*May 14 - 18, 2008 • Orlando, Fl • www.aace.com/meetings/ams/2008/regandprog.php*

*The American Association of Clinical Endocrinologists (AACE) 17th Annual Meeting needs little introduction. As in past years, the four day program will cover a wide range of topics - we're particularly impressed by the focus this year on cardiovascular risk and the metabolic syndrome, CGM, and inflammation. In short, we cannot WAIT for Orlando and the program there! See below for details.*

- **On the morning of May 15, we're looking forward to a talk by Dr. Ralph DeFronzo about the relationship between insulin resistance and atherosclerosis.** We have been hearing more and more about inflammation as a driver of insulin resistance and about the so-called "fat-centric" view of type 2 diabetes, and this session appears to be an excellent opportunity to come up to speed on the topic. The session will also cover the effect of TZDs on inflammation, insulin resistance, and atherosclerosis risk.

- **Dr. Mark Atkinson will give a talk on the morning of the 15th about the pathogenesis and natural history of type 1 diabetes.** He will review recent discoveries and theories about the involvement of environmental factors such as infant diet in the pathogenesis of the disease, and he will discuss newly defined genes that are associated with the disease. The session will be moderated by Dr. Dace Trence.

- **Of late, we've observed a convergence between cardiology and endocrinology, and this convergence will be showcased at AACE.** On the afternoon of the same day, Dr. David Bell will give a workshop about management of cardiovascular risk factors in the diabetic patient. He will specifically discuss the role of diabetes therapies in the prevention of cardiac events and heart failure.

- **The conference includes two sessions on pay-for-performance and other developments in the area of public reporting.** The keynote address, which will be delivered by Dr. Janet M. Corrigan and moderated by the always-profound Dr. Richard Hellman, will specifically discuss key initiatives on the national agenda that may improve safety and quality and the next generation of performance metrics. Dr. Hellman is an expert on this front, as many readers know. In a separate session, Dr. Arthur Lurvey will discuss the development of pay-for-performance as it applies to physician practices and quality development. We look forward to hearing more on the controversial PFP front as this seems especially complicated – and perhaps especially valuable, depending on the physician, in diabetes.

- **We're particularly looking forward to an AACE/JDRF joint session given by Drs. Bruce Bode, Daniel Einhorn, and Darrell Wilson about continuous glucose monitoring.** The session, entitled "Translating Hope Into Reality: Continuous Glucose Monitoring," will review evidence supporting the use of CGM and will discuss obstacles towards the wider adoption of CGM. In a related session, Dr. Philip Cryer will discuss the management and prevention of hypoglycemia, and will review why hypoglycemia is a limiting factor in achieving good glycemic control in diabetes. We love hearing Dr. Cryer speak on this topic and will look forward to hearing his views on CGM and hypoglycemia.

- **Dr. Edward S. Horton will give a talk about diabetes and exercise, and Dr. Ronald Goldberg will discuss management of diabetic dyslipidemia** in "meet the expert" sessions on May 17th.

- **The conference program lists a few fun and active events as well.** Don't miss out on the Exhibitor Wine and Cheese Reception on the evening of May 15, or the Power of Prevention 5k Fun Run early on the morning of the 14th. If you're flying in from the West Coast (as we will be), there's no better way to get over the jet lag.

*—by Mark Yarchoan*

## 9. Diabetes Comings and Goings

- **Chip Hance**, head of Diabetes Care at Abbott, will be taking on another big leadership position on the vascular side of Abbott.
- **Dr. Aaron Kantor** was appointed Chief Scientific Officer of the Immune Tolerance Institute. Prior to joining ITI, Dr. Kantor served as Executive Director of Cell and Molecular Biology for Biomarker Discovery Sciences at Pharmaceutical Product Development, Inc.
- **Matthew J. Pfeffer** was appointed Corporate Vice President and Chief Financial Officer at MannKind. His previous positions were at VaxGen and Cell Genesys.

## 10. DCU Stock Chart and Final Thoughts

Many diabetes stocks improved from a month ago, some quite dramatically, like Sirtris due to the GSK bid, and Insulet and Dex Com and Biodel due to positive news and company progress.

| | 25-Apr-08 | 25-Mar-08 | | 2-Jan-08 | | 25-Apr-07 | | IPO | | Market Cap |
|---|---|---|---|---|---|---|---|---|---|---|
| **GSK** | 45.12 | 43.07 | 5% | 50.17 | -10% | 58.79 | -23% | - | - | 121.47B |
| **NVO** | 67.05 | 68.45 | -2% | 63.80 | 5% | 49.87 | 34% | - | - | 48.73B |
| **AMLN** | 28.54 | 28.70 | -1% | 36.95 | -23% | 42.24 | -32% | 14 | 104% | 3.86B |
| **SIRT** | 22.30 | 12.42 | 80% | 13.00 | 72% | - | - | 10 | 123% | 652.48M |
| **PODD** | 18.16 | 12.79 | 42% | 23.42 | -22% | - | - | 15 | 21% | 500.00M |
| **OREX** | 11.41 | 10.51 | 9% | 13.94 | -18% | 12.50 | -9% | 12 | -5% | 391.47M |
| **BIOD** | 13.51 | 11.04 | 22% | 22.65 | -40% | - | - | 15 | -10% | 318.69M |
| **DXCM** | 7.82 | 4.20 | 86% | 8.95 | -13% | 8.16 | -4% | 12 | -35% | 230.53M |
| **MNKD** | 2.18 | 5.96 | -63% | 7.86 | -72% | 15.47 | -86% | 14 | -84% | 221.10M |
| **HDIX** | 7.65 | 7.46 | 3% | 8.45 | -9% | 11.18 | -32% | 12 | -36% | 136.98M |