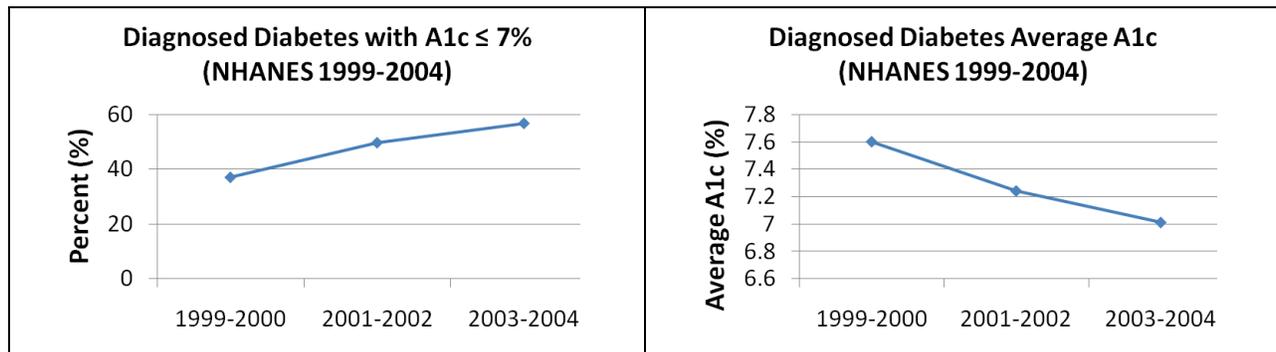


From the Editor

We had barely toasted the New Year when the first bit of good news trickled in for 2008. The January issue of *Diabetes Care* published an article – “Is Glycemic Control Improving in U.S. Adults?” The answer seems to be a resounding yes, though from a relatively poor baseline. As shown in the figure below, the authors, Thomas Hoegur, PhD, and colleagues, mined the very rich NHANES database (a most credible source – we’ve been waiting for the NHANES update and it was like Christmas all over again when we got it) and found that the percentage of U.S. adults with A1cs under 7% has increased from a dismal 34% in 1999-2000 to a much-improved 56% in 2003-2004. The average A1c in this group has been reduced from 7.6% to 7.0%. Pretty amazing!



Why the improvement? We would cite better testing technology (faster meters that require less blood and that are easier to use) and easier therapies to take, which has increased compliance. And the better news is conjecture but... notably, these numbers are only as of 2004, so they don't even reflect easier therapies in Byetta and Januvia. We are betting educational inroads have been made as well. Obviously, no one is declaring victory – almost half of the sample population is still not at the ADA's A1c target – and we think that target level is too high anyway and must come down sooner or later - but at least overall outcomes are clearly improving. As noted, the factors that led to these gains will become even more prominent in the years ahead: better technology and a growing array of therapies.

Interestingly, the percent of patients on insulin continues to drop, from 28% in 1999-2000 to 23% in 2003-2004. The advent of incretins will likely continue this trend – we think many type 2 patients will delay moving to meal-time insulin (or even drop them) and that more incretins will be used with basal insulins.

On the type 1 front, January saw important steps toward the marriage of continuous monitoring and pumps. Insulet signed separate deals with DexCom and with J&J Animas, and although these products probably won't start appearing until 2010, excitement is abounding and the race is on – Insulet and Animas are going after the innovation pioneered by Medtronic. We're moving closer to an open loop or at least greater integration between insulin delivery and glucose sensing – that is compelling indeed, as

I note even my own insulin pump, unconnected though it is from my continuous monitor, is much more powerful and useful with a continuous monitor.

The last big news of January for patients on insulin is that Symlin is now available in a pen – we describe the advantages inside. We continue to see this as a sleeper drug and we're thrilled it's getting easier to use by the way – especially if combined with CGM.

We hope you all had wondrous holidays – till next month! And if you'll be in the Bay Area for ADA Postgrad, please call us!



Kelly L. Close

Major Headlines

DexCom and Animas announce pump/CGM integration deal – page 6
Eli Lilly expresses more Byetta enthusiasm than we've heard in a century – page 9
DexCom and Insulet announce pump/CGM integration deal – page 13
Takeda submitted alogliptin (DPP-4 inhibitor) earlier than expected – page 14
AADE Educator of the year shares passion, insights – page 16

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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/

- **January 17:** When companies talk, symbiosis happens...
- **January 10:** Restoring health to prominence in the healthcare economics debate
- **December 28:** Childhood Obesity – The Shape of Things to Come

Our Revolution Health blog, “Up Close and Personal,” can be found at www.revolutionhealth.com/blogs/kellyclose

- **January 17:** No reimbursement for preventable complications in hospital care
- **January 8:** Support for Pump Therapy Should be Expanded, Not Focused
- **December 27:** Diabetes along the border - the Mexican dilemma
- **December 26:** Opening parents' eyes to childhood obesity: Harder than it looks, but of enormous value

Coming soon in DCU...

ADA Postgrad starts February 1 in San Francisco – very exciting. Around the same time, we’ll be headed to two other meetings – AIDPIT in Innsbruck, Austria, begins January 27, where we’ll get you the update on the artificial pancreas, and the 37th Annual Critical Care Congress in Honolulu, Hawaii, which begins February 2. Stay tuned!

1. Quotable Quotes in Diabetes

"As welcome as the recent favorable trends in glycemic control are, additional efforts are needed to help the ~40% of patients with diabetes who do not have adequate glycemic control."

—Dr. Earl S. Ford and colleagues in an article showing that average A1cs in adults with diagnosed diabetes decreased from 1999 to 2004. The article, entitled "Trends in A1C Concentrations Among U.S. Adults With Diagnosed Diabetes From 1999 to 2004," appears in the January 2008 issue of *Diabetes Care*.

"Exenatide once weekly has an extremely attractive profile and offers the best glycemic control of any diabetes drug ever. Period. It is uniquely positioned to help many people with diabetes take control of their disease."

—John C. Lechleiter, President and soon-to-be Chief Executive Officer of Eli Lilly, speaking bullishly about exenatide once-weekly at the JPMorgan Healthcare Conference on January 8.

"...[Vildagliptin (Galvus, Novartis)] warrants further investigation to explore its full potential in pre-diabetes and would be suitable for testing in future diabetes prevention trials."

—Dr. Julio Rosenstock and colleagues, suggesting that Galvus may be a suitable treatment for pre-diabetes in light of their results indicating that Galvus improves islet function and increases incretin levels in subjects with impaired glucose tolerance. The original article, "Effects of the Dipeptidyl Peptidase-IV Inhibitor Vildagliptin on Incretin Hormones, Islet Function, and Postprandial Glycemia in Subjects with Impaired Glucose Tolerance," was published in the January 2008 issue of *Diabetes Care*.

"We think we have the power to compete very effectively with lap-band surgery."

—Vivus CEO David Teckman, speaking about Qnexa at the JPMorgan Healthcare Conference on January 9. In phase 2 trials, Qnexa caused ~11% weight loss over six months.

"One of our goals for 2008 must be to jumpstart Avandia. The drug deserves to be used... we can counter this clumsy media reporting."

—Jean-Pierre Garnier, Chief Executive Officer of GSK, expressing resentment about the Avandia fiasco at the JPMorgan Healthcare Conference on January 8.

"We're very excited about Actos + DPP-4 inhibition, and that's our advantage compared to Januvia."

—Yasuchika Hasegawa, president of Takeda, discussing the company's plans to bring a fixed-dose TZD (Actos)/DPP-4 inhibitor (alogliptin) pill to market.

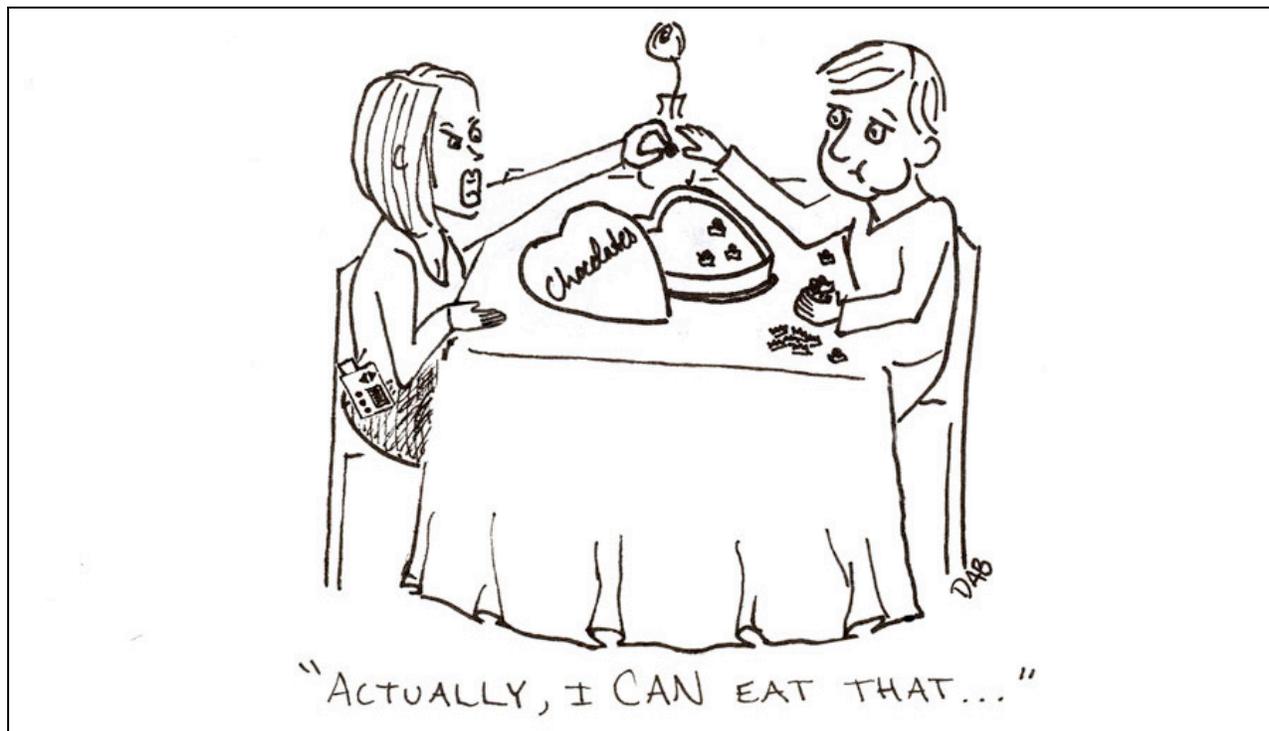
"Alogliptin will be on the market by the end of the year. We haven't seen any safety concerns so far."

—Yasuchika Hasegawa, president of Takeda, speaking optimistically about the prospects of FDA approval for alogliptin. The phase 3 alogliptin data will be released at the ADA annual meeting in June. The company announced the drug's FDA submission on January 4.

"It doesn't matter how great you as a physician may think our product is. If you're in Boston and the Joslin Diabetes Center hasn't heard about the product, you are not going to prescribe it."

—Duane DeSisto, President and CEO of Insulet, speaking at the JPMorgan Healthcare Conference on January 8 about the need to hit key centers across the US in developing the sales force for the OmniPod.

2. diaTribe FingerSticks



-by Daniel A. Belkin

3. DCU Company Watch

- **Diamyd Medical—Positive phase 2b results for Diamyd type 1 vaccine:** On January 21 at the Karl-Stolte Symposium in Hannover, Germany, Diamyd Medical announced positive results of a phase 2b study of its novel diabetes vaccine, Diamyd. In the study, Diamyd demonstrated statistically significant preservation of beta cell function, evidenced by improved insulin secretion both in the fasting and post-meal state, after 30 months compared to placebo. No treatment-related adverse events were noted in the study. The results follow positive data reported at 15 and 21 months of Diamyd treatment. The study enrolled 70 patients aged 10-18 who had been diagnosed with type 1 diabetes within 18 months. The results are sufficient to advance to phase 3 testing, Diamyd Medical noted in its press release. Although we recognize the enormous clinical value of beta-cell preservation even in progressed type 1 diabetes, it is unclear to us what clinical benefit Diamyd's statistically significant results might amount to. We would have appreciated more a quantitative announcement, but we remain optimistic about this vaccine. We look forward to seeing more data in the future.
- **Novartis—Galvus resubmission in US pushed back to 2010:** Galvus was scarcely mentioned during the Novartis 4Q07 earnings call on January 17, and what was said was definitely on the negative side. Discussions are continuing with the FDA on steps needed for approval, but at this point resubmission is not expected before 2010 – so the timeline has moved further out (expectations had been slightly earlier). This means that in the US, Galvus could be the fourth approved DPP-4 inhibitor, after Merck's Januvia, Takeda's alogliptin, and BMS/AZ's saxagliptin – remarkable in our view given that at one point Galvus was poised to be the first DPP-4 inhibitor on the market. Of course we'll see over time how the rest of the class emerges –

it's the early days yet for the DPP-4 inhibitor class, and unexpected toxicities may yet crop up with the competing molecules. In Europe, Galvus has been recommended for use only with a sulfonylurea at a 50 mg once-daily dose and with metformin or a thiazolidinedione at a 50 mg twice-daily dose. The 100 mg once-daily dose will not be available due to concerns about liver damage – this is a negative from our perspective since we think the 100 mg once-daily dose would probably have been the most popular. These dosing changes open the path to formal regulatory approval in Europe, and Galvus should become available to patients in Europe in the first half of 2008. There, Galvus is at a significant disadvantage compared to Januvia because all patients using Galvus will need to have regular liver screening; this spells h-a-s-s-l-e for patients and healthcare providers. We continue to be surprised that this liver toxicity issue came up so late for Novartis.

- **Novo Nordisk—Refocusing efforts post divestment of AERx inhaled insulin:** On January 14, Novo Nordisk announced that it would discontinue development of AERx, the company's inhaled insulin program purchased from Aradigm for \$55 million in late 2004. The decision reflects Novo Nordisk's renewed focus on simpler, more convenient systems for diabetes management, namely long-acting inhaled insulin and inhaled GLP-1 (which we assume are new compounds and in very early stage development currently). Although we believe Novo Nordisk learned from Pfizer's failed foray into inhaled insulin, we believe the company did extensive independent patient research and it has decided to prioritize GLP-1 even higher than it had before. We support this as recent research (Jan 2008 Diabetes Care NHANES piece) shows the percentage of patients on insulin in the US has fallen from 28% to 23%, a trend we believe demonstrates patient preferences for simpler therapies (see our current literature review, page 6). During the conference call, management acknowledged that patients prefer therapy that is once per day or less often and that that was where it was turning its research. A non-recurring cost of ~\$260 million (DKK 1.3 billion) pertaining to the discontinuation of all clinical development and manufacturing activities for AERx will hurt Novo Nordisk's 2007 operating profit. About \$60 million (DKK 300 million) of that cost relates to cessation of clinical trials with another \$20 million (DKK 100 million) for exit costs such as leasing and investment commitments. The rest of the \$180 million (DKK 900 million) pertains to write-down and impairment of tangible and intangible assets and probably to helping the 320 people who have been working on this for so long.

In our view, AERx appeared to be the weakest of the three late-stage inhaled insulin programs left. Whereas both Alkermes/Lilly and MannKind have suggested that their inhaled insulin products will produce significant clinical benefits, Novo Nordisk has never made such a claim for AERx. We also assume that it was easier for Novo Nordisk to bow out than it would be for MannKind and Alkermes/Eli Lilly because both have more advanced programs. Novo Nordisk did stress that its decision on inhaled was not linked to safety concerns – we believe management has probably taken the hardest look at the market from patient and physician perspectives. We wish we could see the research! Overall, we see this news as a negative for others pursuing short-acting inhaled insulins; Novo Nordisk's decision puts more pressure on the remaining two companies to make it a success. At the same time, it means that there will be significantly less competition moving forward. If Alkermes/Lilly and MannKind can get beyond the patient and physician convenience limitations of Exubera, they may well be successful – we continue to believe that insulin initiation by any route, but perhaps especially inhaled, is harder than it looks.

- **DexCom/J&J—Joining the race to combine pump and CGM:** Only days after announcing a development agreement with Insulet (see below), DexCom announced on January 10 that it will also work on CGM development with J&J's Animas. In our view, this is positive for both

companies, for industry, and for patients. We think DexCom's open platform approach is smart and that development with Insulet and Animas will move quickly. Importantly, the two deals will enable DexCom reps to talk specifically about how much CGM improves pump therapy – we think this is one of the biggest positives about CGM to date.

At the JP Morgan Healthcare Conference on January 10, DexCom CEO Terry Gregg further discussed the company's development agreements with J&J/Animas and Insulet regarding the integration of DexCom CGM technology into Animas and Insulet pumps. In both agreement deals, the DexCom receiver will be eliminated in the combined CGM/pump device and all CGM data will be displayed on the Animas pump and Insulet Personal Diabetes Manager (PDM), respectively. DexCom estimates that the integrated DexCom/Animas device will be available in 2009 or early 2010. The company will receive \$750,000 from J&J/Animas toward development, clinical, and regulatory expenses.

We note that this move will give J&J solid initial footing in the CGM market without having to dedicate substantial resources to developing the technology in-house. DexCom gets exposure to the Animas patient base – a major plus. In addition, CGM will get wider exposure overall – a plus for tight glycemic control and diabetes care in general. Of all the powerhouses in diabetes, it appears most logical to us that J&J would eventually acquire DexCom, and this deal may ultimately be the first step in that direction.

In both deals, DexCom's partner (Animas or Insulet) will hold primary responsibility for sales and marketing and will still be responsible for all technical support related to the insulin pump aspect of the integrated device. DexCom maintains all revenue from sales of the disposable CGM sensors and will be responsible for CGM support for patients. DexCom will lead all regulatory testing, trials and filings for future generations of the device with its partners in a supporting role.

Gregg also delivered an update on the next generation DexCom CGM device. The new generation promises to have improved trending information, a new algorithm, and smaller geometry. The new algorithm is said to be “designed for improved performance” including improved trend screens and meal/exercise/dosing markers. A pivotal clinical trial was just completed in December 2007 showed non-inferiority to the DexCom SEVEN. DexCom voluntarily decided to delay filing for premarket approval-supplement (PMA-S) until late 1Q08 or early 2Q08, however, in order for post-pivotal R&D efforts to produce modified third-generation sensors that will be cheaper and more effective than the current ones.

According to DexCom, in-hospital CGM may provide a market opportunity worth over \$500 million given that the biggest barrier to tight glycemic control is fear of hypoglycemia – a critical niche where trending information from CGM could be invaluable. Gregg pointed to four landmark studies showing the benefits of tight glycemic control in a hospital setting and highlighted a statistic from the Society of Critical Care Medicine that estimates that 28% of US hospitals have adopted tight glycemic control protocols, with another 17% currently underway. We believe the importance of keeping an eye on this market lies in the idea that the artificial pancreas in its most elemental form will likely first be developed in this setting. It is critical that CGM companies pay close attention to this market to help speed innovation and progress toward a cure. We are slightly skeptical about the data on the percentage of hospitals pursuing tight glycemic control but definitely agree that this is a very important market given the extremely high needs.

Finally, DexCom will expand internationally and on this front will initiate clinical trials outside the US in 2008. Animas already has a European presence, which should help DexCom.

- **Vivus—Bold claims about long-term Qnexa weight loss:** During the Vivus presentation at the JP Morgan Healthcare Conference on January 9, CEO David Teckman focused almost entirely on Qnexa, one of several products the company is developing. In a phase 2 study, Qnexa caused an average of 10.6% weight loss over the course of six months, and weight continued to decline even at the end of the trial. Impressively, the Qnexa arm of the study had a 92% completion rate, and no serious adverse events were reported. Mr. Teckerman said that he believes the efficacy will be “much greater” in a longer trial and that Qnexa will compete effectively with lap-band surgery – bold claims in our view. Mr. Teckerman spent much of his presentation touting the safety profile and tolerability of Qnexa. The drug is composed of phentermine and topiramate – both well studied and FDA-approved drugs. One thing that we found intriguing was Mr. Teckerman’s focus on treating diabetes with Qnexa. He said that Qnexa had demonstrated some weight-independent effects on diabetes, and that the company would actively pursue a diabetes indication. There was a brief mention that patients enrolled in the 28-week Qnexa OB-202 study for type 2 diabetes would be allowed to continue the study for an additional 28 weeks (the extension study is DM-230). We view this as a strong indication of Vivus’s focus in the diabetes arena. The data from OB-202 will be presented at ADA.
- **Arena—APD668 put on hold to test more potent compound - negative in our view:** At the JPMorgan Healthcare Conference, Mr. Lief briefly discussed Arena’s diabetes drug candidates, in partnership with Ortho-McNeil. The company’s lead diabetes compound, APD668, was put on hold after phase 1 results were completed. Mr. Lief said that the phase 1 results were successful in that they validated the drug target, but he said that Ortho-McNeil wants to evaluate a similar but more potent drug before advancing APD668. This new GDIR-targeting drug will move to the clinic at the end of 2008. Although Mr. Lief sounded very optimistic about the clinical data on APD668, we consider the discontinuation or holding of this drug as a clear negative; it suggests the clinical data were not convincing and did not justify advancing the drug. It is great there is another compound but the timing on it is a setback by any assessment.

Most of Mr. Lief’s presentation focused on lorcaserin, in development for the treatment of obesity. Given the drug’s mechanism in targeting the 5-HT_{2c} serotonin receptor, there has been an ongoing safety concern about valvulopathy. Mr. Lief underscored that there has been no apparent increase in valvulopathy in the lorcaserin clinical trials, and that the drug is extremely selective in its binding; he said lorcaserin will be filed in the latter part of 2009. In our view, the drug’s efficacy is somewhat underwhelming. Mr. Lief said that about 30% of patients treated with the highest dose achieved 5% or more weight loss – much less than many other obesity drugs currently in phase 3 development. We think lorcaserin may have greater efficacy if combined with phentermine, though we suspect that this combination would be a difficult one to study or pursue. Safety will naturally be critical in drug development of any obesity compound and this is important particularly for the earlier – stage compounds.

- **Alkermes—Continued confidence in Lilly and Amylin partnerships:** At the JPMorgan Healthcare Conference, Alkermes CEO David Broecker characterized Lilly as an ideal partner and cited Lilly’s experience with the insulin market as an important asset for both products that Alkermes is helping to co-develop: exenatide once-weekly and AIR insulin. During the breakout session, Mr. Broecker said that AIR insulin would have a different fate from Pfizer’s discontinued Exubera because a more experienced player in the diabetes market will introduce it with better data. He acknowledged that reimbursement would depend on their ability to demonstrate clinical benefits over other forms of insulin, and he seemed confident on this front; we look forward to seeing more data. We were impressed by the small size of the AIR insulin device, which he held up in front of the audience. The device was small enough to palm with one hand. Unsurprisingly,

Mr. Broecker appeared to be most excited about exenatide once weekly, which he described as having “unprecedented” clinical trial results. We would agree, particularly the contrast in side effects compared to currently available therapies. Alkermes will provide Amylin with the technology required to manufacture exenatide once weekly, but will not actively participate in the manufacturing of the drug.

- **Enteromedics—Attempting to fill the gap between gastric bypass and pharma:** At the JPMorgan Healthcare Conference, CEO Dr. Mark Knudson provided a very broad overview of EnteroMedic’s product in development, called the Maestro System. The product uses electrical stimulation to intermittently block the vagus nerve, increasing feelings of satiety from the stomach (for more background, see Company Watch, Diabetes Close Up #75). Dr. Knudson described the product as filling the gap between current pharmacotherapy (less effective, less invasive) and surgery (highly effective, highly invasive). New data from the VBLOC-RF2 feasibility study shows that the treatment is associated with 29.5% weight loss after nine months of therapy. Management said that the Maestro System will likely cost about \$20,000, with an additional \$8,000-\$10,000 for the implantation procedure for a total cost of ~\$30,000, which seems high compared to other obesity devices. Dr. Knudson also said in the breakout session that J&J’s recent entrance into the vagus nerve blocking space is “a good thing” because it will likely to call attention to the area.
- **GSK—Frustrated and trying to jumpstart Avandia:** It’s no secret that Avandia sales have spiraled downward since Dr. Steven Nissen published a meta-analysis showing an association with myocardial infarction. At the JPMorgan Healthcare Conference, GSK CEO Jean-Pierre Garnier said one of the company’s efforts moving forward would be to attempt to jumpstart Avandia sales. He expressed some optimism that the dust was settling and Avandia sales would begin to pick up mid-way through 2008. Mr. Garnier seemed to be somewhat bitter during his presentation, calling the Avandia fiasco an “American phenomenon” advanced by “clumsy media reporting.” He explained that in Europe, Avandia sales have actually increased over the past year, and he announced that there is no reason to use the competitor’s drug over Avandia. We note that regardless of concerns about myocardial infarction, Actos has a better lipid profile than Avandia. Without strong data to counter existing doubts about the drug, GSK will be hard-pressed to convince physicians that it is the better choice of the two. Mr. Garnier described GSK’s pipeline as being the most robust in the entire industry, and he expressed optimism that the company would have up to 25 product launches before the end of 2009.
- **Eli Lilly—Strong focus on Byetta and exenatide once-weekly:** At the JPMorgan Healthcare Conference, President and soon-to-be Chief Executive Officer John C. Lechleiter gave a broad overview of Lilly’s strategy and ambitions. Notably, over half his presentation focused on Byetta and exenatide once-weekly, and he did not make a single mention of insulin (except AIR). Mr. Lechleiter made very bullish statements about exenatide once-weekly, calling it “the best diabetes drug for glycemic control ever, period.” Some of the advantages he highlighted included outstanding glycemic control, substantial weight loss, minimal risk of hypoglycemia, convenient once weekly dosing, no titration, lower rates of nausea and well-tolerated injections. Mr. Lechleiter said that the phase 3 data meet the requirements for an NDA, and that several comparator trials (superiority trials, no less) against a TZD, DPP-4 inhibitor, insulin, and metformin are in the works. At the conclusion of his talk, Mr. Lechleiter reviewed his goals as new CEO of Lilly. He said his top priority is to increase the flow of new products from the pipeline. Other goals are engaging customers in new ways, driving productivity, and developing leaders.
- **MannKind—Differentiating TI from Exubera, confirming NDA filing in 2008:** During the JPMorgan Healthcare Conference, management continued to work to differentiate

Technosphere Insulin (TI) from Exubera, underscoring that unlike Exubera, TI will offer true clinical advantages because it has a pharmacokinetic profile that best mimics the body's own physiological response. Management reconfirmed that phase 3 data should be available this year and an NDA filing before year-end. Management also mentioned that the lung issues seen with smokers and Exubera were a product of higher lung porosity in smokers. MannKind is in "advanced partnering discussions" – we assume a partnership may happen after phase 3 data are shown, but not before then. CEO Al Mann briefly promoted the early-phase GLP-1 compounds; highlighting their rapid bioavailability and 0% rates of nausea and profuse sweating.

- **WebMD—Growing acceptance of the Internet as an educational tool:** At the JP Morgan Healthcare Conference, CEO Wayne Gattinella spoke about online market growth and discussed the ways in which WebMD is further developing its online services. Gattinella said that the Internet has become the primary source of information in health inquiries (ahead of doctors), and 40% of doctors use the Internet on a daily basis for information pertaining to their practice. There is a trend emerging wherein doctors are fully accepting the Internet as an educational tool for their own patients, as currently 75% of physicians proactively recommend websites to their patients. Gattinella emphasized the accuracy of the content on WebMD sites and mentioned new technologies the company has launched in order to better serve patients, including technology that is more interactive and personalized. There is \$25 billion in spending each year related to companies marketing/educating consumers and professionals. Gattinella shared that WebMD is looking to grow the corporate side of the business from 112 large clients today. While the discussion was by no means directly diabetes focused, we see this resource as a necessary part of patient education and empowerment – in a recent patient survey we did of 850 of our diaTribe (www.diatrube.us) readers, 48% said they used WebMD sometimes or often for diabetes news, which put the site in third place out of eleven for online diabetes resources – only dLife and the American Diabetes Association ranked higher.
- **Orexigen—Phase 2b Empatic data show 14-15% weight loss over 48 weeks:** New data released before Orexigen's presentation at the JPMorgan Healthcare Conference showed that Empatic is associated with ~14-15% weight loss over 48 weeks. Discontinuation in the trial was described as being similar to placebo; we would have appreciated clarity on this front as well as more demographic baseline information; certainly at first glance the data are impressive. As a reminder, Empatic is a combination of the generic drugs bupropion and zonisamide. Orexigen's lead product, Contrave, is a combination of the generic drugs bupropion and naltrexone. Contrave is slated for a 2010 product launch, while Empatic will likely be commercialized in 2013.

CEO Dr. Gary Tollefson explained that Empatic and Contrave will be marketed in a way that makes them complementary rather than competitive with one another. Contrave will be presented in the marketplace as a drug that targets food cravings and helps women in particular to find control. Empatic will be presented as a pharmaceutical alternative to surgery, causing 15% or more weight loss. Dr. Tollefson said he is not especially concerned about generic substitution with either Empatic or Contrave. Generic substitution would provide poorer formulations and require more complicated titrations. We agree with Dr. Tollefson's statement that the threat of generic substitutions is largely overblown. The question/answer session was brief and focused on the issue of partnerships. Dr. Tollefson said that Orexigen is open to the idea of partnerships for Empatic as early as this year; however, the company will not wait for partnerships. We note that Orexigen would need to license Empatic to a company with a direct to consumer advertising program and a large primary care sales presence. Orexigen may look for international partners outside the US.

- **Biodel— Making the case for more rapid acting insulins:** At the JPMorgan Healthcare Conference, Dr. Solomon Steiner, CEO and Chairman of Biodel, reviewed the milestones achieved by the company this year and spoke enthusiastically about the prospects of VIAject, an injectable prandial insulin. Dr. Steiner spent much of the presentation explaining that VIAject has a more rapid course of action than any other available rapid-acting insulin. The words are compelling – if in fact VIAject does work more quickly than competitive rapid-acting insulins and is just as good in other important respects, we believe it would be an extremely valuable tool for patients. Dr. Steiner underscored the need for more rapid-acting insulins, because current insulins inadequately mimic first phase insulin release. Dr. Steiner said that the average person who uses prandial insulin has 1.2 severe hypoglycemic events per year, and this is a significant deterrent for patients to go on insulin. He noted that more rapid acting insulins will require lower dosage, cause less hyper/hypoglycemia, and will provide safer therapy overall; payors will likely be willing to reimburse for more rapid insulins, though not necessarily at a premium in our view.

Biodel has ambitious plans to file VIAject in December of 2008. VIAject will be offered in several forms: VIAject A, to be sold in markets with adequate cold chains (such as the US, Europe and Japan), is a liquid that can be refrigerated or frozen. VIAject B, for sale in markets without adequate cold chain distribution, is a two-vial presentation (lyophilized insulin and proprietary VIAject diluent), which is stable at room temperature. Both VIAject A and B will be offered in 100 IU/CC and 25 IU/cc sizes in both vials and cartridges. The company hopes to also release VIAject pens, with 1 IU or ¼ IU dose increments. The company is planning a manufacturing facility to formulate, fill and finish the liquid presentations. On the partnership front, we assume Biodel would look to work with a company with real global reach and one with diabetes (if not necessarily insulin) experience but no official word on this yet.

- **Bayer—“Rebuilding diabetes care market share, investing in the brand”:** During the Bayer presentation at the JPMorgan Healthcare Conference, management spoke positively about its Diabetes Care business, pointing out that it is rebuilding market share, investing in the brand, and looking to shorten product lifecycles. The company’s goal is to have 75% of the product line be three years or younger in 2009. The company is looking to be the "partner of choice" (as a reminder it announced an exciting deal last year to supply Medtronic Diabetes with blood glucose strips overseas) and expects two to three percent above-market growth (which it estimates at six to seven percent).
- **Sirtris—Positive phase 1b results announced for SRT-501 (resveratrol):** New and encouraging data from a phase 1b study of SRT-501, Sirtris’s lead product candidate, were released at the JPMorgan Healthcare Conference. The two doses - 2.5 g and 5.0 g - of SRT-501 were both found to be safe and well-tolerated, causing no dose-related adverse effects. Although the study was designed primarily to assess the safety and tolerability of SRT-501, the results showed a statistically significant improvement in OGTT over the 28 days of treatment. CEO Christophe Westphal had previously indicated during the 4Q07 earnings call that no such changes were expected because of the short duration of the study (due to the mechanism involved, it takes a while for SIRT1 activation to have a therapeutic effect though it is not yet clear how long); we see the news as a strong positive for the prospects of SRT-501. SRT-501 has been characterized as “weak” by the company relative to its new chemical entities (NCEs), and there has been a somewhat open question whether SRT-501 would be abandoned in favor of developing the NCEs. Given the new data, Sirtris is likely to continue developing SRT-501 as an add-on to metformin. Dr. Westphal also hinted at the JPMorgan meeting that the new data suggest that SRT-501 may be quite effective in monotherapy.

Dr. Westphal described SIRT1 activation as a possible first-line therapy for diabetes or pre-diabetes. So far, all data have indicated that SRT-501 or the NCEs are convenient, safe, have high tolerability, don't cause weight gain or hypoglycemia, reduce inflammation, and are effective at lowering blood glucose as well as reducing insulin resistance. Of the currently available oral drugs for diabetes, only metformin has this profile – and for many, metformin actually isn't that tolerable due to the GI effects (which can be managed, say some specialists). Prior to the Dr. Nissen controversy, TZDs had seemed headed for first-line therapy or pre-diabetes use, but concerns about safety have made this idea a long-shot, to say the least. We do think Januvia, once-weekly exenatide, and the weekly version of liraglutide could well hold promise in pre-diabetes as well, assuming that long-term safety data are eventually amassed.

- **Amylin—Optimistic outlook for Symlin, exenatide once-weekly:** At the JPMorgan Healthcare Conference, President and CEO Dan Bradbury discussed Amylin's 2008 plans with the mantra "challenging science and changing lives," citing the need for Amylin's "game-changing products" in the current diabetes arena. Bradbury said that the launch of the SymlinPen should boost sales of \$61 million for the latest 12 months (LTM) ended 3Q07 (up 65% from 3Q06). Introduction of the SymlinPen will make the drug more convenient to use for the 1.3 million mealtime insulin users in the US, and Bradbury expressed optimism that this convenience would translate to a major opportunity to advance Symlin sales. We must point out, however, that the drug is still pretty complicated to take because of dosing and because insulin must be reduced when taking it. Nonetheless, we see the emergence of the pen as a major advantage for current and future Symlin users.

Once-weekly exenatide was characterized as the drug producing "the best glycemic control and best weight loss observed in a pivotal study of any diabetes drug ever... period." Both Bradbury and John C. Lechleiter, President and soon-to-be Chief Executive Officer of Eli Lilly, Amylin's partner in the development of exenatide LAR, alluded to this quote in their remarks for their respective companies. Superiority trials comparing exenatide LAR with TZDs, DPP-4 inhibitors, insulin glargine, and metformin, respectively, may allow Amylin to regain stronger footing with endocrinologists and diabetologists. Bradbury described one trial, initiating this quarter, as a blinded controlled study comparing once weekly exenatide to pioglitazone (TZD) and sitagliptin in patients on metformin background therapy. The second trial will be an open label superiority study comparing once weekly exenatide to insulin glargine as add-on to oral antidiabetic (OAD) therapy. The results for both studies are anticipated for 1H09. The final trial will be a blinded study comparing LAR to metformin. Each study will enroll between 400 to 500 participants.

Bradbury gave an interesting analysis of Byetta uptake trends among HCPs that pointed to some pressure from the introduction of DPP-4 inhibitors. In a WKH July 2005 - October 2007 graph showing trends in Byetta prescriptions, he attributed initial strong uptake of Byetta (launched July 2005) to specialists whom he characterized as "early adopters," whereas later adopters (mainly PCPs) were more sluggish on the uptake. In late 2006/early 2007, there was a marked cooling-off in the rate of monthly prescriptions in the "early adopters," which he attributed to the initial launch of a DPP-4 inhibitor. However, there was an increase in the rate for "later adopters," which comprises a much larger sector of the market – 80% of prescriptions. He added that this was positive for the introduction of exenatide LAR. Bradbury also reported prescription growth of Byetta prescription among primary care physicians (PCPs), which we believe is a pretty solid testament to the drug's ever-growing potential for success – PCPs provide about 80% of Byetta prescriptions. Total prescriptions were up 33% in 2007 over 2006. Positive study results with focus on glycemic control will buttress monotherapy indication submission for Byetta in 1H08 – target approval in 2H08. The study, published in the January 2008 Clinical Therapeutics Journal,

showed that Byetta offers glycemic control comparable to insulin glargine with the added benefit of decreased risk of hypoglycemia and weight loss. The study showed ~60% of participants reached the target of <7% A1c with weight loss similar to previous Byetta studies.

On a different front, Bradbury said that a phase 2b study for pramlintide and metreleptin combination therapy will be initiated in 1H08. Pramlintide is an analog of human amylin and metreleptin is an analog of human leptin. The combination has shown a 12.7% loss in body weight over 24 weeks (average reduction of 25 pounds from start of study). Bradbury touted the established safety track-record of both molecules as pivotal to the company's goal of creating a drug that achieves long term weight loss without compromising patient safety. No updates were given for the company's 2nd generation amylinomimetic obesity drug candidate.

- **Insulet/DexCom—Developing combined pump/CGM together, positive for both:** On January 7, Insulet announced that it had signed a development agreement with DexCom to integrate DexCom's continuous glucose monitoring (CGM) system into Insulet's wireless, handheld OmniPod System Personal Diabetes Manager (PDM). The PDM with integrated DexCom technology will program the patient's OmniPod with insulin delivery instructions and will also display continuous glucose readings from the DexCom sensor. We expect that this will be a useful device for patients who have been waiting for an option to use a disposable pump with a CGM. We also believe that more patients would be inclined to use a pump and a CGM if they have only one item to carry around to control both. Launch of the product is slated for mid-2009, though we would not be surprised to see it sooner.

The agreement between DexCom and Insulet is non-exclusive, and we assume both companies are continuing to work on the open platform model, which healthcare providers in particular will applaud given that some patients want to choose various parts of different systems. Insulet is also working with Abbott as we understand it on CGM, and we assume the agreement is unaffected by the recent announcement between Animas and DexCom. From the perspective of Insulet, the agreement with DexCom seems particularly smart because there are various other insulin delivery "patch" or "disposable" products swirling around in development; Medingo said recently it expected to launch its pump in 2008 (we assume late 2008).

The Insulet/DexCom agreement is one additional small step toward the goal of a closed-loop system. Medtronic continues to push toward a closed-loop system as well, and it clearly is working on future generations of its combined pump/sensor – its R&D and clinical expertise is known to be very strong and certainly it has a big head start. For the Insulet/DexCom combined pump/sensor system, simplicity will be important for swaying physicians and educators to adopt yet another system; both Insulet and DexCom have positive track records on this front. A simple combined pump/sensor from DexCom/Insulet might be tough competition for Medtronic in a way that current offerings from DexCom and Insulet are not.

- **Amylin—SymlinPen now available, potential boost to sales:** On January 7, Amylin announced that the rollout of the SymlinPen 120 and the SymlinPen. The FDA approved the Symlin Pen at the beginning of October 2007, and we believe that the pen, in contrast to the syringe and vial, could increase the appeal for the drug significantly. The pen is more convenient since it is easier to teach and simpler to use from both a dosing and an application perspective. The pen-injector devices have fixed dosing that deliver the drug Symlin to help improve glucose control during mealtimes. SymlinPen 120 can deliver 60 or 120 micrograms of Symlin per dose and is targeted at type 2 patients; SymlinPen 60, is geared for the type 1 market, and can administer Symlin in increments of 15 micrograms, (maximum of 60 micrograms) per dose.

From a commercial perspective, we believe the new pen injection will boost sales – how much depends on how well the company markets the pen. Ease of teaching should bode well for prescriptions since we are all well aware of the decreasing amounts of time that endocrinologists have to spend with their patients.

We believe that at least some patients held off on trying Symlin until the pen came out, but the challenges with Symlin administration in terms of dosing still remain. While this is a chance for another launch in some respects, we believe that it will also be important for the company to make sure patients have the right education on the drug. We were able to put our hands on one of the first pens available in California and recently began testing it. Unfortunately, the drug is not approved for use in pregnancy and it does not look like it is on the horizon given the liability associated with testing in this group. That said, the post-prandial control that Symlin provides could be just what the doctor ordered for pregnant women whose recommended A1c range is 5.0% - 5.5%.

Though the drug is still complex, we believe that the SymlinPen will be a useful new device for patients – it is now more portable and easier to take for patients “on the go.” In addition it does not have to be refrigerated. The side effects will not change with the pen – nausea is still a problem for some. One negative may be that the smallest dose is 15 micrograms, whereas with a syringe and vial, one could begin with an even smaller 5 microgram dose; this may limit the drug for some patients.

- **Takeda—New drug application submitted for alogliptin, earlier than expected:** On January 4, Takeda announced that it had submitted a new drug application (NDA) to the FDA for alogliptin, its DPP-4 inhibitor candidate. This happened a bit earlier than had been expected; Takeda previously stated that the submission would take place sometime in 1H08. The company has completed six pivotal phase 3 studies with a total of over 2,000 patients at more than 200 centers worldwide. Takeda has applied for a monotherapy indication as well as add-on indications with metformin, thiazolidinediones, sulfonylureas, and insulin. Alogliptin will likely be the second approved DPP-4 inhibitor in the U.S., after Merck’s Januvia and before Novartis’s Galvus and BMS/AZ’s saxagliptin.

At the JPMorgan Health Care Conference, Yasuchika Hasegawa, president of Takeda, was quite bullish about the prospects of the company’s recently filed DPP-4 inhibitor. Mr. Hasegawa said that there have been “no safety concerns” and that the efficacy of the drug is similar to Januvia, though a true head to head trial is needed to compare efficacy accurately. He also said that most of the clinical data will be released at the ADA annual meeting in June. Importantly, Mr. Hasegawa expressed excitement about a fixed-dose Actos/DPP-4 inhibitor combination, and he said that this will secure Actos sales after the Actos patent expires in early 2011. We think that a lower-dose Actos/DPP-4 inhibitor will be critical for Takeda and will help the company break into the DPP-4 inhibitor market. In our view, the combination of Actos + a DPP-4 inhibitor is likely to be very effective, and if a lower fixed dose of Actos is used in the combination, the side effect profile would likely be better than Actos alone (less weight gain and edema). However, we note that Actos + a DPP-4 inhibitor will not likely provide a truly synergistic mode of action, because the TZDs and DPP-4 inhibitors have entirely different mechanisms of action. By contrast, Janumet (Januvia + metformin) is a truly synergistic combination, where the effect of both agents together is greater than would be expected from the drugs alone. This is because metformin increases the total level of GLP-1, whereas Januvia increases the amount of GLP-1 in the active form. These two mechanisms work together to increase GLP-1 activity.

The DPP-4 class of drugs has come under some scrutiny recently; Merck's Januvia had a recent label change to acknowledge a possible association with exfoliative skin disorders including the rare but potentially fatal Steven Johnson's syndrome, and Novartis's Galvus remains stalled at the FDA because of "skin-related" findings and more recent concerns about liver toxicity. That Takeda has seen "no safety concerns" in its alogliptin program is encouraging; we look forward to confirming this when we see the phase 3 data ourselves. Although the DPP-4 class has many advantages, particularly with regards to tolerability and convenience (no GI issues, no hypoglycemia, no weight gain, no fractures, no CNS issues), safety remains a question in the long-run with the entire class. With alogliptin's submission and the expected submission of saxagliptin (BMS/AZ) very soon, competition in the DPP-4 class is heating up, though Merck retains first mover's advantage. That said, we imagine that Takeda will compete well in the DPP-4 space by pursuing an Actos/alogliptin combination pill, particularly with its vast patient experience with Actos. If anything, Takeda has only been weak on marketing in our view.

- **Bayer—Voluntary recall for Contour TS Meter Strips, no major fallout expected:** On December 21, Bayer Diabetes Care issued a market recall of test strips used with the Contour TS blood glucose meter. The company reported that new equipment used during the initial rollout of the test strips caused the initial lots of the strips to display blood sugar readings that are elevated by 5-17% above the actual blood glucose levels. Although the 5-17% potential error isn't within the range of what Bayer finds acceptable, we wouldn't foresee any commercial or regulatory problems stemming from this. While most strips today from the top manufacturers are probably under 10% error, as we understand it, for the FDA's requirements they can be up to 20% off. A total of about 50 lots of strips are affected (perhaps between 15 and 25 million strips).

The Contour TS is a new meter that is not widely distributed globally and uses different strips from Bayer's main meters, the Contour and the Breeze. Although Bayer hasn't made sales public for the three brands individually, we believe the Contour TS strips represent a very small percentage of total strip revenue for Bayer, likely well less than 5%. The recall doesn't affect the Contour or the Breeze.

The Contour TS ("Totally Simple") meter was approved in late September in the US and is distributed for mail order only. Globally, various rollouts began in select countries at the end of summer including Turkey, France, Austria, Korea, Mexico, and India. The meter has "no coding" technology, which Bayer pioneered several years ago, a 0.6 µl blood sample size, and eight-second readout of blood glucose results. Overall, Bayer is acting responsibly, recognizing that patients with elevated blood glucose readings who are on insulin (about 30-50% of patients) will take too much insulin and be at risk for hypoglycemia. A 100 mg/dL reading could read as high as 117 mg/dL or a 200 mg/dL reading could read as high as 234 mg/dL. In either instance, it is unlikely that the insulin taken would vary significantly. Although all recalls are costly, we believe on balance that the cost here is relatively low given the small impact on Bayer's total strip inventory, and that the recall is important for Bayer to maintain its reputation for high quality and reliability.

- **JDRF—\$150 million secured for one-year extension of Special Diabetes Program:** On December 19, Congress passed a Medicare spending bill that included a one-year \$150-million extension of the Special Diabetes Program, allowing critical type 1 diabetes research to continue. Although the JDRF may have hoped for more than a one-year extension of the program, the short extension comes as a relief in one of the most difficult years for diabetes research funding. National Institutes of Health (NIH) funding for diabetes research has gone down significantly since its peak in 2003. Similar to other NIH divisions, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has seen its success rate for funding of research grants

fall from over 30% in 2003 to around 20% (this means only one in five research proposals in the division that includes diabetes research are now granted funding). That the Senate and House passed the extension of the Special Diabetes Program even in a difficult budget environment shows that lawmakers view diabetes as a priority; it also reflects the strength of Larry Soler and his stellar Washington team who we believe fought to the wire on this one. The JDRF will continue to advocate for the Special Diabetes Program and hopes to secure a multi-year renewal of the program next year.

- **Glucolight–Improvements to Sentris-100 non-invasive meter:** On December 18, Glucolight unveiled several design and performance improvements to its Sentris-100 glucose monitor. The new version of the Sentris-100 meter is about half the size and weight of the original, and the sensitivity of the sensor to blood glucose is also improved. The Sentris-100 uses optical coherence tomography (OCT)-based technology to measure physiological targets within the dermis that correlate to changes in blood glucose level. In other words, the monitor shines a light on a person’s skin and then monitors the absorption of a spectrum of light that is sensitive to glucose concentration to determine glucose concentration in the blood without the need to break skin. The monitor can sample blood glucose every 30 seconds. Sentris-100 is not yet commercially available and is being developed only for the acute care environment. GlucoLight completed its first “clamping study” and ICU clinical study of Sentris-100 earlier this year.

In our view, the recent ergonomic and functionality improvements are important for the busy and cramped ICU environment. The present version of Sentris-100 is similar in size to an IV pump and is similarly pole mounted. Glucolight believes that the monitor will offer cost-savings to hospitals by making the process of measuring blood glucose more efficient. Sentris-100 requires no manual intervention after an initial calibration. Glucolight is now preparing for another round of clinical studies in 2008. We laud these accomplishments and are enthusiastic about the company’s progress, although we note that non-invasive monitoring has been a historically disappointing area of development, as it has been difficult for companies to develop a device that is accurate, easy to use, and portable.

—Kaku Armah, Rachel Cameron, Kelly Close, and Mark Yarchoan

4. Interview with Teresa Volpone, AADE Educator of the Year

It is always wonderful to see somebody rewarded for a lifelong dedication to a good cause, and Teresa Volpone is no exception. A diabetes educator and provider at Virginia Mason Medical Center in Seattle since 1990, Ms. Volpone is known and admired for her compassionate work as a diabetes educator, pharmacist, and patient advocate. For her dedication and excellence in diabetes education, the American Association of Diabetes Educators (AADE) named Ms. Volpone National Diabetes Educator of the Year in 2007. Ms. Volpone is the first pharmacist ever to receive the award; we applaud her and are delighted that she was rewarded with such a high honor for her contributions. We were privileged to have the chance to speak with Ms. Volpone recently and to get to her thoughts on the various treatment options for people with diabetes and the biggest barriers to improved patient care.

Kelly: Thank you so much for taking the time to speak with us. To begin with, do you think you could tell us a little about how you got interested in diabetes education?

Teresa: In 1977, when I was still in training as a student, there was an elderly woman who came into our pharmacy. She got syringes and insulin and didn’t have the faintest idea what to do. It was immediately clear to me that if I knew about insulin and I knew about giving injections, I would actually be able to help her. That was the pivotal point in becoming interested in diabetes.

Kelly: What brought you to Virginia Mason?

Teresa: Well, a number of years ago I got a call from Virginia Mason saying that they wanted to open a pharmacy in a new clinic building right next door to the endocrinology department, and they really wanted to have full service for people with diabetes. So, I moved there to open and manage that pharmacy. We really tried to have everything that could possibly be needed for a person with diabetes – both the products and the knowledge to use them so that if someone was sent to the pharmacy for a monitor, we would be able to teach them about blood glucose monitoring: what their goals were, how to do it, how to use the results... the whole service.

After a while I wanted to go back to working directly with the patient in managing their care, not just in teaching them about the tools. This was probably about 1995. I said, “I really think we should have some type of protocol for hypertension and lipid management, because that’s where the doctors, the experts, don’t have enough time.” So I started getting referrals of patients for cardiovascular risk reduction.

Kelly: Wow, you were way ahead of your time.

Teresa: Yes, well, that’s how I started working more intensively with the patients in the clinic. Then I thought, “You know, now that I’m seeing these patients, I can see that they’re really not adequately controlled with their blood sugars. Since they’re already right here in front of me, what about teaching them how to adjust their oral meds, or their insulin, or whatever is necessary?” So that became part of the visit.

Kelly: That’s really interesting because it speaks to how relatively new self-management and insulin adjustment is.

Teresa: But I think Virginia Mason has been doing that for a long time. We were always thinking about how to put control in the hands of people with diabetes instead just having them wait for us to tell them what to do. And we’ve also changed with the times. When I first worked there we had week-long classes that included management, foods, and everything. And the physicians are very active participants.

Kelly: Do you still have the week-long classes, or is it a problem now where people can’t get that reimbursed?

Teresa: People were not getting reimbursed so we have been moving toward shorter classes. Just recently, we initiated a class that’s been very, very condensed to just two days.

Kelly: What do you think about that?

Teresa: I’ve always thought that the most important part of class was actually the hands-on food/nutrition education. And in two days they don’t really get much practice with that.

Kelly: This is incredibly unfortunate and all too common from our perspective. Why do you think that this is not getting paid for anymore? It seems so counter-intuitive.

Teresa: Well, sometime before 1991, I remember Medicare did a survey of education programs, asking about the number of hours, the topics covered, etc. And then, not too long after, there came out this statement about the ten hour reimbursement, and I think it was based on an average of the types of programs that people actually had at the time. Virginia Mason, at that time, had a 32-hour program, but it was way different than any other program.

Kelly: Maybe you could talk more broadly about the different types of education that patients are getting out there, and what is reimbursed and what’s not, and where you think we need to go from here.

Teresa: In this area we have about six or seven programs but because of reimbursement, they tend to be similar in length. We only have one pharmacy that has started to look into providing education for patients. There aren’t ADA-recognized pharmacy-based education programs here yet but there

are other community pharmacy-based programs across the country that are ADA recognized. In the long term, having programs that are within the community may be better for reaching more people.

Kelly: Do you tend to focus more on cardiovascular or microvascular complications? We often hear that long term complications aren't really *real* to some patients.

Teresa: I think that everybody is very aware of heart disease and stroke. They can identify with those things a little easier than with microvascular disease. Also, there's more that they can do in terms of, "Here's a medication we can use to treat your hypertension." Sometimes I worry about blood glucose testing because it can be very negative for some people. A big reason that people often don't test is because they don't want to see their results.

Jim: Do you give the patient who is ready a clear game plan? For example, "If we want to lower your blood pressure, you do things X-Y-Z."

Teresa: Yes. Usually I will say, "These are the options; Let's do this as far as the blood pressure, and here's what we would ultimately like to see, because we know this reduces your risk of stroke." I use stroke a lot, because it seems to mean more to people than having a heart attack. They think, "I'll just go in and get fixed," if they have a heart attack.

Kelly: Does Virginia Mason operate at a profit? The reason that I ask this is because it seems like a lot of the really good diabetes clinics operate at such an incredible loss.

Teresa: I don't believe we operate in the black. The reimbursement is pretty poor. And for pharmacists, no matter how intensive the appointment is, no matter what we've done, the highest that can be billed is the very lowest fee. For a long time I thought that people who had hypertriglyceridemia, and were overweight, and had hypertension should be monitored carefully for diabetes. And then the next thing you know, someone put a name to it, and now we're talking about the metabolic syndrome. Once that came out, we actually designed a class in conjunction with our Heart Attack and Stroke Prevention Clinic. And, of course, it was absolutely not reimbursed. Nobody reimbursed for preventative lifestyle.

Kelly: But why?

Teresa: Well, you know the old story is that insurance companies don't look into the future; they just look at what their costs are at the moment. It goes back to getting into our legislatures and saying this has got to change. There's got to be a push on insurance companies or on general programs, community programs, to change perspective

Kelly: Well, we worry about it from the perspective of how there aren't enough people going into endocrinology, there aren't enough people becoming diabetes educators, and there probably aren't enough people becoming pharmacists with a focus on diabetes. From that perspective, it just seems like we're headed for a very dangerous time – or really, we're in one, and just don't realize the extent of this. Who could do anything about that? Is it government? Is it industry?

Teresa: Good question, Kelly, and I really don't know the answer. I was just at a technology meeting and I thought, "I'm just going to ask everybody here if they want to come work at Virginia Mason," because we were trying to recruit some endocrinologists. And every time I talked to somebody they said, "You know what? We're trying to recruit somebody too."

Kelly: Very depressing from a patient perspective – and it should be, too, from a taxpayer perspective because this just means more people will receive less care and suffer more long-term complications. This is a crisis if anything is. Shifting gears a bit, because I'm not sure I can continue on that depressing front, do most of your patients know what their A1c is?

Teresa: Most of them don't know the term specifically. I would say probably 95 percent of them know that there's a test that's done and that we talk about. Interestingly, the newly diagnosed people seem

more likely to know that number. The ADA and everyone has also done a much better job of putting diabetes in front of people.

Kelly: Wow. Ninety five percent know there's a test but most don't know the specifics. I wonder how that relates to treatment. There are so many more new classes of drugs now than there used to be. Can you talk about the complexity of the field?

Teresa: I sometimes tell patients in our class, "Well, if I were talking to you in 1994, we would just be talking about some types of insulin, and one type of pill, and that would be it." The wider selection of drugs today, in addition to lifestyle changes, should allow us to help patients reduce long term complications either by reducing blood sugars or through other ancillary drug effects, and hopefully with fewer side effects. I actually think there are a *growing* number of pharmacists who are interested in diabetes.

Kelly: That's a relief that at least somewhere the interest is growing!

Teresa: That's true. Bigger institutions, like Rite-Aid, are starting to look at this. There have been a lot of certificate programs trying to provide education to pharmacists that have been fairly well attended; and pharmacy organizations have supported programs for training pharmacists to learn more about diabetes.

Kelly: It makes sense, especially because pharmacists can add so much value in diabetes – it's intellectually so interesting and they don't suffer from poor reimbursement as doctors and CDEs do – that's not to say they don't do an amazing job and shouldn't be paid more! Can you talk about some trends at Virginia Mason? Are there more people on insulin, or are there more people on some of these new classes like GLP-1 or DDP-4 inhibitors?

[Comment here: Pharmacists are poorly reimbursed for non-dispensing services. In the last few years Medicare has instituted something called Medication Therapy Management and created billing codes for these services, but it is unclear, as yet, what reimbursement will be on this set of codes. On the dispensing front reimbursement is also poor – a reason that many small neighborhood pharmacies are unable to continue in business.]

Teresa: For type 2s, we're seeing more bedtime insulin and we've seen a fair use of GLP-1 (exenatide) as well. I know some of our primary care providers use GLP-1 (exenatide) in maybe 30 percent of type 2s. We have used exenatide in our clinic, but we are somewhat selective about who we choose for exenatide. We tend to use it in the overweight patient with marked elevations in postprandial blood sugars despite reasonable nutritional intake, but our usage relative to the number of patients seen is quite low. I don't really have a handle on sitagliptin yet. We continue to use very little sitagliptin. And of course we have metformin and sulfonylureas.

Kelly: You know, people sometimes complain about the side effects associated with sulfonylureas, and when we saw the ADOPT trial presented last year, they said about 40 percent of the people on metformin had some kind of side effect, mostly GI related we gather. Is it because the doses aren't right or it's not titrated correctly...? Can you talk a bit about side effect profiles and whether any of the new drugs have improved on that front?

Teresa: I think the 40 percent with metformin sounds about right to me, as far as my experience goes. Some of it is probably titration, but I think people usually are able to get to a higher dose if they are titrated slowly. I think sometimes we use a higher dose than is necessary.

Kelly: I think in the ADOPT trial they used the maximum dose.

Teresa: I don't think we know that someone has to be on 2,000 mg of metformin. Maybe it would actually be beneficial to keep them on 1,000 mg. And there is some evidence that using 2500 mg daily is of no added benefit.

Kelly: What about the other drugs?

Teresa: Well, with Byetta, you're looking at a least 40 percent who have some nausea.

Kelly: Are they more willing to endure the nausea because there is the potential for weight loss?

Teresa: Yes. As a matter of fact, you sometimes have to tell them, "Don't worry if you're not having nausea. It's okay, it's still working." Remember how we talked about motivation? Weight loss, to many people, is very good motivation. That's a cultural norm. We don't want to be heavy. They are willing to put up with the nausea unless they become really, really sick.

Kelly: With the long-acting version of Byetta that's being developed, the nausea seems to be considerably less. How do you trade that off versus the gauge of the needle, somewhere in the range of potentially 25 or 26?

Teresa: I think most people are really, really concerned about needle use. The two reasons people don't want to use insulin is because they're afraid of the needle and afraid that they're going to drop so low that they'll pass out and die. Usually once they've had their first injection, they realize it's not as bad as they thought. They may not like it but they're able to do it.

To answer your question, if it's once a week, I think people could get over it. I don't think a 26-gauge needle would be a limiting factor. Right now, Becton Dickenson has the one-time use needles where you don't even see the needle, and I think seeing it is the main issue for most people.

Kelly: You mentioned that the primary care doctors at Virginia Mason are pretty engaged with people with diabetes and I wonder if you could talk about that a little bit more. Are they actually putting people on insulin and Byetta?

Teresa: I think that we have worked really hard to set up a system that helps the primary care provider. On our website we have protocols for starting insulin and oral medicines and what the best path might be for doing that, and information about the different medications that we have, and a template for diet. We have a visit template that serves as a memory check to make sure they go over everything – the A1c, the micro, the potassium.

Kelly: That's amazing – our system seems so tough. It's a lot for the primary care providers to do all this in these eight-minute sessions...

Teresa: Well, we have nurse/physician teams in our primary care clinics. So actually the nurse will see the patient first, and will do a lot of the preliminary set-up before the physician comes in to see the patient. A pharmacist is part of the team as well. Sometimes when there are multiple medications issues, the patient may see the pharmacist before they go in to see the nurse/physician team. We have condensed the path that the physician has to go through. So in our clinics we're seeing physicians starting patients on insulin. Sometimes they'll send them to us for the education portion and for the initial two weeks of follow-up, and then they go back to the primary provider and continue from there. They are starting Byetta and combinations of medications. They can't all come to endocrinologists, particularly when there are so few coming out of school.

Kelly: Do you think primary care doctors find it easier to put people on a GLP-1 because there's no hypoglycemia associated with it? You mentioned the two big problems being fear of needles and hypoglycemia.

Teresa: I think that they probably like that idea a lot. They also like the idea that there's weight loss, because they've probably been talking to these people for years about losing weight.

Kelly: From the trend, it looks like endocrinologists really, really like GLP-1 but primary care has been a littler harder to win over – though actually more recently that trend is changing and PCPs are more open to Byetta.

Teresa: I think there are always regional differences. That might be true for the whole United States, but in our department we started using exenatide as soon as it was released. We tracked our patients to see what happened and whether it really looked like what the company was telling us would happen – and it worked as well as reported. One of our issues was insurance coverage – that was probably the primary reason people wouldn't start it. The cost was there. But otherwise, it really performed pretty much the way it's marketed.

Kelly: And what about Januvia? We know many would love to have your thoughts on this drug.

Teresa: My personal experience, and therefore my opinion, is limited. We have had a couple of leaner people on it and it doesn't seem to be as impressive. But I think the number of people I've used it in is too small to really tell. I will say that as far as instructing somebody, it's a lot easier to tell somebody how to take Januvia than what to do with Byetta. There are phone calls, you know, about what's going on with exenatide - adjustment of sulfonylureas if they are taking them, dealing with the nausea, etc. I think it is trickier. As of early 2008, we have not had a surge in prescribing Januvia and it remains third line.

Kelly: Do you have data on the differences in A1c changes, adherence, etc?

Teresa: When we have used sitagliptin we have not seen as dramatic changes in A1c. If insurance covers the medication people seem to take it as easily as any other medication. Once again my personal experience is not extensive.

Kelly: Regarding insulin, are the mealtime insulins much more complicated than the Lantus once-a-day types of insulins?

Teresa: Insulin is used by over 50% of the patients we see in endocrinology. More than 50% of drug cost for our patients with diabetes has been and continues to be for insulin. If you're just talking about acceptance, it's easiest to start with an evening dose of long-acting insulin. There are people who can do well on that, say, in a type 2 population. It's pretty easy, because most of the time the risk of low blood sugar is going to be pretty minimal with type 2s. People don't have to take it with them during the day and you can usually demonstrate an improvement in morning blood sugar with patient-activated titration - if somebody starts insulin, they want to see something happen. Regarding the mealtime insulin, I have this idea that certain individuals actually might do better with something like a combination of Byetta and a long-acting insulin. I don't have any data on this yet, though.

Kelly: We definitely heard a lot of that as well from many of the leading endocrinologists. What about the trend toward lowering post-prandial blood glucose? How important do you think that is?

Teresa: I do believe controlling post-prandial blood sugar is more important than we assume, but I'm sort of stymied about what the best way to do it is. It is clearly a critical piece to achieve. If we really think people's blood sugars have to be optimal, the only way we're going to get there is by addressing the post-prandial blood sugar as well. There's no way to get around it. I think maybe the DPP-4 inhibitors or the GLP-1s might be part of the answer.

Kelly: I wonder if you have an opinion about the endocannabinoids and rimonabant?

Teresa: I don't know what to make of them. When I saw the side effect data I thought, "Whoa! Now there's something you don't necessarily want people to have." (Depression, suicidal thoughts.) It makes me wonder about the mechanism. You're messing around with the central nervous system. I'm interested in what happens in Europe, because they're selectively using it. Maybe there's some derivative of it that may be useful. But we don't really understand what's going on. But then I think we probably don't understand even 30 percent of what is going on in diabetes.

Kelly: Yes, because of the complexity. I wonder if you could talk about how you feel about the TZDs after this whole Avandia fiasco.

Teresa: Funny you should ask. A while ago I was just chatting with my coworker, and she said, “You know, I wonder if sulfonylureas are dead.”

Kelly: That’s so funny; we were going to ask you that question.

Teresa: I don’t think they’re dead yet, but I think they will be. If it weren’t for the current controversy about the thiazolidinediones, I would say we’d be saying goodbye to the sulfonylureas. We know that they help lower the A1c, but they don’t have as much longevity before a second drug is added. And when you look at outcomes ratios, the major area of benefit in the UKPDS was microvascular disease - specifically retinopathy.

Kelly: Oh, is that right? That’s interesting, I didn’t realize that.

Teresa: At this point in time we can’t kill them yet, because we only have so many tools and we know that they have a long history and do have some benefit. But maybe we should just revisit the products (sulfonylureas) that are currently available. There may be an edge of one product over another. We should look at how we’re using them and whether some are safer than others.

Kelly: What do you think will happen with Actos and Avandia?

Teresa: I think they’ll be exonerated. That’s what I think.

Kelly: That’s interesting – how do you mean?

Teresa: There’s the “signal” of increased ischemia, but I think when we keep looking at longer term studies that it’s going to be less of an issue. When I read the initial publication I just kept thinking, “I’m not sure I can just buy into this.” If you throw out studies where people didn’t report problems, are we somehow changing our numerators and denominators? And what about the studies that are still in progress? Can we just ignore those? Maybe I’m wrong, but that’s what I was thinking.

Kelly: We heard that there was some pressure from NIH on FDA because of the RECORD trial and other really big trials. The implications of saying that a drug shouldn’t be on the market are obviously extremely negative on an ongoing trial.

Teresa: It is difficult because if you know that you have all these people on a drug that is being called “bad”, then you know those folks are going to start to wonder. So they did the right thing in the interim analysis. As an aside, I never was a fan of Avandia for reasons I can’t even elucidate.

Kelly: Is that because of the lipid profile?

Teresa: Yes, mostly. If you were to ask me which one to use, I would probably say that I recommended Actos.

Kelly: Yet both of them are basically \$3 billion drugs. Do you think that Avandia has done so well historically because of marketing?

Teresa: Oh, yes. Oh, yes.

Kelly: Would you recommend that type 1s try continuous monitoring? Is that something that you guys have had many patients on?

Teresa: Yes. We probably have two dozen people who have their own real-time monitoring devices. But we do have about eight people a month who will come in and we’ll do the blinded continuous glucose monitoring for them with the MiniMed CGM. We definitely see more and more inquiries regarding insurance ... The sensor we use for blinded monitoring is similar to the Guardian and the Paradigm Real-time system. It’s pretty simple, though a little cumbersome because the CGMS used in blinded monitoring still has the cord attaching the device to the sensor site - but I think that’s just to keep people from losing it.

Kelly: Is it mostly type 1s who do this?

Teresa: We've done it in both, but mostly type 1s. Oftentimes we do it because we can't figure out why their home blood sugar readings are so perfect and their A1c's just don't match up. We'll have them check fasting and postprandial, but I think everybody's learning that a two-hour postprandial blood glucose doesn't come close to when people's blood glucose is actually the highest. And it's really hard to have someone evaluate nocturnal blood sugars. So we find the CGMS really helpful for figuring out what's really going on and designing something that works for this person. Actually I wish we could do it on more people.

Kelly: That's brilliant. It's almost like advocating for personalized medicine. You can plan a much more targeted regimen.

Teresa: Right. I think it's an absolutely fabulous tool and everybody who's ever done it has seen the value of it. Except for someone whose sensor site fails; then all you get is garbage. Otherwise it really can be a very useful teaching tool and therapeutic tool.

Kelly: Do you generally change the treatment program of someone who goes on CGM?

Teresa: Yes. I would say that 95 percent of the time we make a change. Sometimes you can't make a change because you don't have the tool that allows you to make a change – like needing to go on an insulin pump.

Kelly: It sounds like it gives you more specific information so you have a sense of how changes might work.

Teresa: Well, if I had to pick a technology, continuous glucose monitoring at home has huge value for many people, especially those who don't sense their lows. To me that use is a no-brainer. I think insurance companies should be covering sensors for persons with that issue. If you had an easily acceptable format where you could just put it on and wear it – of course now you still have to do some blood glucose checks and some data entry calibrations – it would be a fabulous tool. I know people who put patients on pumps and then start them on a sensor and it sure makes tremendous sense to me.

Kelly: Before we finish up, I was wondering if you could talk about what was it like for you to receive the Educator of the Year Award at AADE.

Teresa: It was a total surprise. I'm very humbled by it. I feel it's a huge responsibility. I think of it as a way to honor the people I work with and the patients who work with me.

Kelly: That's wonderful. Congratulations again, and thank you so much for taking the time to speak with us.

-- Kelly Close and James S. Hirsch

5. Conference Pearls: Metabolic Diseases World Summit

November 1-2, 2007 • San Diego, CA • www.confabb.com/conferences/41292

This was a very small conference – about 25 people attended, and most of the people at the meeting were presenting. Even though the conference was small, we were impressed by the quality of the presentations and by the wide variety of perspectives and topics. Presenters hailed from academic institutions as well as industry (Merck, Lilly, Nasteck, Sirtris, Metabolex, ChemGenex, Amgen, and others). Topics included everything from insulin therapy to beta cell transplantation, mitochondrial function, and the metabolic syndrome.

- **Three of the presenters (Charles Alexander of Merck, Dr. Ann Murphy from UCSD, and Jerry Colca of Metabolic Solutions Development Company) argued very convincingly that the TZDs exert their positive effects on insulin resistance through improving mitochondrial function, rather than acting on PPAR-gamma.** We were

interested to learn that there is little correlation between the strength of PPAR-gamma binding and the efficacy of the TZD (for example, Avandia binds to PPAR-gamma ten-fold more than Actos, and yet they are equally effective at improving insulin sensitivity). The effects of TZDs are too rapid to be explained by transcriptional events. Finally, PPAR-gamma knockout mice still show benefit from TZDs. Together, this evidence suggests that the TZDs are acting elsewhere. The real, pharmacological target of TZDs may be a small region in the outer mitochondrial membrane called MitoNEET. Mr. Colca went on to say that an “ideal” TZD would not even bind to PPAR-gamma, because PPAR-gamma activation has many negative effects including fat cell size/mass increase and bone loss.

- **One highlight of the conference was the “panel discussion,” which quickly developed into an open microphone discussion.** The audience seemed to agree on a number of topics: 1) In situations where it is hard to figure out why patients are in poor control, continuous glucose monitoring (CGM) can be very helpful. The example case given by Dr. George Dailey of the Scripps Clinic in La Jolla, CA, was a 14-year-old patient on intensive insulin therapy with an A1c of 10% who improved significantly on CGM. 2) Interestingly, many of the clinicians expressed disappointment that more type 2 patients do not use insulin, pumps, and CGM. Since this was not a technology-oriented conference we found this particularly positive in terms of what the future may hold for these technologies as they become much easier to prescribe, use, and analyze. 3) There was a consensus that patients who have been using inhaled insulin (Exubera, recently discontinued) with good results are unlikely to resist moving to injected insulin. Pump therapy should be the first choice for children who were using inhaled insulin.
- **Nastech and Metabolex both justified their lead compounds – nasal insulin and MBX-102, respectively.** Dr. Richard Mitchell from Nastech Pharmaceuticals showed that nasal insulin is well tolerated, has high bioavailability, a short time to action, and a short duration of action (arguably reducing hypoglycemia). Nasal delivery is broadly applicable, and bioavailability of nasal administration is high. Nasal insulin in phase 1 trials had about 30% bioavailability compared to subcutaneous delivery. Our main questions still center on absorption and overall predictability. Brian Lavan of Metabolex showed that its lead compound, MBX-102, causes similar improvements in insulin resistance as Avandia and has robust anti-inflammatory activity. However, it does not cause significant weight gain or edema. We will be very eager to see whether long-term trials corroborate early findings – clearly agents that work on insulin resistance are sorely needed, as this is usually the initial defect in pre-diabetes or early diabetes.
- **The well-known and very highly regarded Dr. Aaron Vinik discussed the importance of treating the underlying causes of diabetes through increasing beta-cell function and mass.** Notably, he encouraged greater clinical use of GLP-1 analogs and TZDs for the protection of beta cells. Dr. Vinik is noted for his work on diabetes complications, especially neuropathy, so we find his views particularly interesting since he has a clear goal to prevent complications in patients. Dr. Vinik explained that conventional models of treating diabetes do not attempt to change the underlying biology of disease. Eventually, all type 2s will look like type 1s because they lose about 4% of beta cell function every year. People with type 2 diabetes have a beta cell volume that is 63% reduced on average compared to a person who does not have diabetes. Beta cell loss begins long before a person has diabetes – people with pre-diabetes have a beta cell volume that is reduced by 40% on average. In order to increase beta-cell mass, it will be necessary to produce beta cells at a faster rate than they die. It is impossible to “fix” diabetes unless the problem of insulin secretion and beta cell mass is corrected. Although it wasn’t discussed, this raises questions of the importance of therapies to treat pre-diabetes or at least to delay progression of pre-diabetes. Although 2007 was a negative year overall in terms of late-

stage development of compounds for pre-diabetes, as the TZDs suffered a major hit, we are positive about prospects for other classes for this indication.

- **Dr. Domenico Accili also argued that diabetes treatments should attempt to increase beta-cell function and mass, rather than increasing beta-cell secretion directly.** He put forward what seems to be an increasingly widely-held view that increasing beta-cell secretion, which is the mechanism of action of the sulfonylureas, may actually speed up beta-cell dysfunction rather than slow it down – obviously a real negative of SFUs, in addition to increased hypoglycemia and weight gain. The incretins are particularly exciting, he said, echoing the sentiments of other speakers, because they may help to preserve beta-cell function.
- **Dr. Angelina Trujillo discussed how the goal of insulin therapy for gestational diabetes is to maintain near normal pre- and post-prandial glucose levels throughout pregnancy** using a basal bolus regimen with multiple injections or continuous insulin infusions (i.e. pump therapy). The most important takeaway in our view was that she absolutely believes that glucose normalcy should be the norm in pregnancy and that the goal for pregnant patients should be an A1c of 5% or less. We believe this may be possible with continuous glucose monitoring and a very close watch of levels – these goals aren't for the faint of heart, however, in our view, and they reinforce for us how better communication and education are needed to highlight the importance of extremely tight glucose control in pregnancy. We believe the percentage of pregnant women achieving post-prandial scores of 120 mg/dL or less and A1cs of 5% or lower is likely very low – this should clearly be a goal, however, given the potential complications of high glucose levels.
- **At the end of the conference, there was a scintillating session on mitochondrial function and aging.** One of the theories that was widely discussed in this session is that mitochondrial dysfunction is the basis of the metabolic syndrome. This mitochondrial dysfunction is driven by excess calorie intake, leading to increased reactive oxygen species. Mitochondrial dysfunction increases with age, which is one reason the prevalence of the metabolic syndrome increases with age.
- **Dr. Murphy said that the oxidative capacity (maximum ability to produce ATP) of mitochondria declines with aging and is evident in diabetic, insulin resistant, and obese patients.** Mitochondrial ATP production is critical to glucose-stimulated insulin secretion. When mitochondria aren't functioning well, there is insufficient production of ATP, leading to poor glucose uptake and insulin resistance in tissues throughout the body, including liver, adipose tissue, and skeletal muscle. Reactive oxygen species (H₂O₂) damage mitochondria and inhibit their ability to produce ATP. Mitochondrial dysfunction from reactive oxygen species increases with age. The amount of reactive oxygen produced is greatly increased with sedentary lifestyles. The hypoxic signal from exercise is a signal for increased mitochondria biogenesis, which is why exercise reduces insulin resistance; pharmacologic agents such as sirtuins and TZDs may also increase mitochondrial biogenesis.

—By Mark Yarchoan

6. Literature Review: A1c Trends in the US from 1999-2004

In the January 2008 volume of Diabetes Care, Dr. Earl S. Ford and colleagues report on A1c trends among U.S. adults with diagnosed diabetes using data from the National Health and Nutrition Examination Survey (NHANES) 1999–2004. Among participants with diagnosed diabetes, the percentage of participants with an A1c of 7% or less increased from about 37% in 1999-2000 to 56% in

2003-2004 (an improvement of nearly 20%). Similarly, the average A1c of participants with diagnosed diabetes decreased from 7.6% to 7.0% over the same time period. Overall, the study provides compelling evidence that glycemic control is improving on the national scale, though there is still considerable room for improvement. In our view, the higher percentage of patients reaching the American Diabetes Association (ADA) treatment goal of 7.0% suggests that it is time for the ADA to lower the target goal to 6.5%. One of the possible reasons that the ADA has not lowered targets thus far is because current targets are not being met, but with a higher percentage of patients at goal than in previous years it may be time for the ADA to reevaluate its suggested target.

- **The authors of this study used data from the National Health and Nutrition Examination Survey (NHANES) 1999–2004 to examine A1c trends among U.S. adults with diagnosed diabetes.** NHANES is a highly respected and statistically powerful nationally representative sample of over 13,000 U.S. adults. Participants in the study were asked if they had been diagnosed with diabetes or pre-diabetes. All participants also had A1c measured using Primus CLC330 and Primus CLC385 instruments. The study did not distinguish between type 1 and type 2 diabetes and was therefore unable to provide separate estimates of A1c trends for type 1 and type 2 diabetes patients.
- **Approximately 30% the participants who had diabetes were undiagnosed.** Among participants found to have diabetes, the percentage that had been diagnosed was 70.2% in 1999–2000, 68.5% in 2001–2002, and 74.6% in 2003–2004.
- **The percentage of patients with diagnosed diabetes with an A1c of 7% or less improved significantly from 1999-2000 to 2003-2004.** In 1999-2000, only about 37% of participants with diagnosed diabetes had an A1c of 7% or less; by 2003-2004, approximately 56% of participants had an A1c of 7% or less. The improvement in percentage of patients at the ADA goal of 7% is encouraging and comes after a long period (1988–1994 to 1999–2000) when the percentage of patients with an A1c of 7% or less remained stable at slightly under 40%.
- **The average (unadjusted geometric mean) A1c of patients in the U.S. with diagnosed diabetes also improved significantly from 1999-2000 to 2003-2004.** In 1999-2000, the average A1c was 7.6%; in 2001-2002 the average A1c was 7.2%, and by 2003-2004 the average A1c had improved to ~7.0%.
- **Consistent with previous studies, the present study found significant ethnic disparities in A1c.** In the most recent NHANES, the average A1c for white Americans was 6.8%, compared with 7.4% for African Americans and 7.8% for Mexican Americans. Interestingly, women had slightly lower average A1cs than men – 6.8% vs. 7.1%.
- **Overall, the present study provides strong evidence that diabetes care is improving on a national scale.** However, there is still considerable room for improvement. Given that many more Americans are achieving an A1c of 7% or less, this may signal to the American Diabetes Association that it is time to lower the A1c treatment goal to 6.5%, in line with the IDF, EASD, and AACE. In our view, one of the reasons that the ADA has not lowered targets is because it feels that current targets are not being met. It is likely that there will be increased pressure to lower treatment goals after the ACCORD study is published. The present study did not indicate what percentage of people with diabetes in the U.S. have an A1c of 6.5% or below, or 6% or below, but we believe that it is probably a very low percentage.
- **The positive trend in glycemic control nationwide is good news for industry as well as patients.** With diabetes patients living longer with more tightly controlled glucose, the total number of years that the average person with diabetes will continue to take medication will

increase and the diabetes market will continue to expand. The many new drug therapies that have arrived recently may be one reason that A1cs continue to fall, and we hope the trend will continue for years to come.

—by Kelly Close and Mark Yarchoan

7. Conference Preview: Society Of Critical Care Medicine 37th Annual Critical Care Congress

February 2-6, 2008 • Honolulu, Hawaii • www.sccm.org/annual_congress/

At Close Concerns, we always look forward to the annual Society of Critical Care Medicine meeting because this conference is *the* place to get up to date on tight glycemic control in the hospital. This year, it's a real win as well because the meeting is in Honolulu with a special session on tight glycemic control in nearby Kauai! Here are sessions we would recommend to those also interested in this topic:

Sunday, February 3

Starting at 8:15 am on Sunday, there is an entire session on tight glycemic control moderated by Dr. Stanley Nasraway from Tufts University. Sessions include the following – we definitely wouldn't miss the first one by Dr. James Krinsley of Stamford Hospital in Connecticut, one of the top thinkers in this field. We will be interested to hear from Dr. Clifford Deutschman who apparently hasn't been swayed that tight glycemic control is very relevant; we expect his discussion to focus on medical ICU patients, which is a more controversial population than surgical ICU patients in terms of the demonstrated benefits of tight glycemic control. New guidelines may also be out, which would be exciting since we see the current fairly fragmented approach that hospitals have taken as one of the biggest difficulties in adopting tight glycemic control. More on hypoglycemia will be key to hear from the moderator.

- *Tight Glycemic Control Is Still Relevant* - James S. Krinsley, MD, FCCM - **8:15-8:35 AM**
- *Tight Glycemic Control May Not Be Helpful* - Clifford S. Deutschman, MD, MC, FCCM - **8:40-9:00 AM**
- *ACCM's Clinical Practice Guidelines For TGC* - Judith Jacobi, PharmD, FCCM, BCPS - **9:05-9:25 AM**
- *Hypoglycemia And Other Obstacles To TGC* - Stanley A. Nasraway, MD, FCCM - **9:30-9:50 AM**
- *How Should Blood Glucose Be Measured?* - Amado X. Freire, MD, MPH, FCCM - **9:55-10:15 AM**

Also on Sunday morning is a short talk on a very important and under-addressed sub-population of hospital patients: pediatrics.

- *Tight Glycemic Control: What Do We Do In Children?* - Vinay M. Nadkarni, MD, FCCM - **8:35-8:55 AM**

Afterwards, we highly recommend the following afternoon session on obesity. Though not directly related to tight glycemic control, we're very interested in hearing about the impact of the obesity epidemic on intra-hospital care.

- *Epidemiology And Outcomes* - Stanley A. Nasraway, MD, FCCM - **12:35-12:55 PM**
- *The Pathophysiology of Morbid Obesity* - Philip S. Barie, MD, MBA, FCCM - **12:55-1:15 PM**
- *Pre-op Eval. And Intra-operative Management* - Louis Brusco, Jr., FCCM, MD - **1:15-1:35 PM**

Tuesday, February 5

More on obesity! It's an early session, but worth catching for anyone interested in the field. We assume that Dr. Erstad will be discussing the dosing of drugs more generally, but we'd be interested to see if he addresses the dosing of diabetes or obesity drugs specifically.

- *Effects Of Morbid Obesity On Dosing - Brian L. Erstad, PharmD, FCCM - 6:30-6:50 AM*

Wednesday, February 6

Wednesday will be a big day with a morning session involving many interesting questions and another debate featuring Dr. Krinsley. We're interested to hear about perspectives on whether we should have a glucose control standard at this point; certainly it would help hospitals interested in adopting more intensive glucose control to establish practical, easy-to-implement protocols for doing so. We hope to hear about the in-hospital potential for continuous glucose sensors and non-invasive sensing devices in Dr. Grant Bochicchio's update on glucose measurement technologies; we believe that critical care will be an important market for CGM devices going forward.

- *Overview of Glycemic Control in Critical Care - Simon Finfer, MD - 8:00-8:40 AM*
- *Setting a standard for glucose control - 8:50-9:30 AM*
 - *Moderator: Michael J. Murray, MD, PhD, FCCM*
 - *We have sufficient data - James S. Krinsley, MD, FCCM*
 - *We need more data - Simon Finfer, MD*
- *Glucose Measurement Technology - Grant Bochicchio, MD - 9:50-10:15 AM*
- *Case Management Discussion: Glucose Control in Specialized Patient Populations - 10:15-11:00 AM*
 - *Clarence Chant, PharmD*
 - *Gail Cresci, MS, RD, RD, CNSD*
 - *Jean Charles Preiser, MD, PhD*
 - *E. Daleen Aragon, PhD, CCRN, FCCM*
- *An Overview of Metabolic Regulation and End-organ Dysfunction - Mervyn Singer, MD - 11:00-11:40 AM*

Friday, February 8

The meeting will finish up with some key sessions on Glycemic Control & Metabolic Dysregulation on Friday morning. We're curious about whether insulin, which is believed to have anti-inflammatory effects, will be featured in the discussion on modulating inflammation and the stress response. As well, we'd be interested in whether tight glucose control is discussed in the session on outcome disparities.

- *Novel Clinical Modulators of Metabolism: What you can do in your ICU - Paul Wischmeyer, MD - 8:00-8:40 AM*
- *Nutraceuticals Improve Outcome During Severe Critical Illness - 9:00-9:50 AM*
 - *Moderator - Douglas B. Coursin, MD*
 - *PRO - Paul Wischmeyer, MD*
 - *CON - Michael J. Murray, MD, PhD, FCCM*
- *Case Management Discussion: Modulating Inflammation and the Stress Response - 10:10-11:00 AM*
 - *Gail Cresci, MS, RD, RD, CNSD*
 - *Mervyn Singer, MD*
 - *E. Daleen Aragon, PhD, CCRN, FCCM*
 - *Clarence Chant, PharmD*
- *Why Outcomes are Different in my Part of the World? - 11:00-11:45 AM*
 - *Moderator - Michael J. Murray, MD, PhD, FCCM Simon Finfer, MD*
 - *Mervyn Singer, MD*
 - *James S. Krinsley, MD, FCCM*
 - *Jean Charles Preiser, MD, PhD*

—by Kelly Close

8. Final thoughts

There are no comings and goings this month that we know of. In stock news, it's clearly been a tough month – we never recommend stocks to buy but at these low levels there are certainly some that look promising.

	18-Jan-08	18-Dec-07		2-Jan-08		18-Jan-07		IPO		Market Cap
GSK	50.43	50.89	-1%	50.17	1%	55.75	-10%	-	-	138.88B
NVO	59.63	62.46	-5%	63.80	-7%	41.92	42%	-	-	40.19B
AMLN	33.55	37.47	-10%	36.95	-9%	40.67	-18%	14	140%	4.52B
MNKD	7.30	8.60	-15%	7.86	-7%	16.46	-56%	14	-48%	736.69M
PODD	20.78	22.94	-9%	23.42	-11%	-	-	15	39%	549.22M
BIOD	19.25	20.32	-5%	22.65	-15%	-	-	15	28%	384.86M
SIRT	13.41	14.06	-5%	13	3%	-	-	10	34%	388.10M
OREX	12.50	14.30	-13%	13.94	-10%	-	-	12	4%	336.38M
DXCM	8.90	7.67	16%	8.95	-1%	8.53	4%	12	-26%	251.83M
HDIX	8.08	7.65	6%	8.45	-4%	11.89	-32%	12	-33%	145.55M

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