DIABETES CLOSE UP

Diabetes Close Up
September 2006, No. 61
DREAM on…

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

From the Editor:

If you thought summer was busy for diabetes... get ready for an intense autumn. Conferences, product approvals, new indications, and reimbursement drama all stand before us, and it's as stirring as ever – probably more so. We leave today for EASD and Copenhagen and DREAM (see inside for more on this highly anticipated pre-diabetes trial), and we cannot wait to hear what the experts have to say about pre-diabetes and the potential to prevent the disease with TZDs. The TZD class, of course, isn't without its controversy – DCU editor and writer Jim Hirsch and I were lucky to have an oh-so interesting discussion on the topic of TZDs with Dr. Lois Jovanovic and Dr. Bob Henry – see page 10 to really dig in. It sounds like a 50 percent reduction in the rate of progression to diabetes in the treated groups would be considered a win for TZDs. Now, the background rate of diabetes in this population will be a key question – stay tuned for DREAM results and please watch our subscriber-only blog next Friday, September 15, for news as it unfolds.

Dr. Anne Peters the Great! We'll have more on this next month in DCU #62, but in the meantime, set your TIVOs for October 5 and PBS's Remaking American Medicine. The diabetes epidemic is once again taking center stage, this time as part of this striking four-part PBS series. The ambitious effort focuses on clinicians trying to take a closer look at transforming the health care system – among them, the inspiring Dr. Anne Peters, who has diabetes clinics in Beverly Hills as well as East Los Angeles and is turning her nurses into diabetologists to improve patient care. Model for the country? It's the best we've seen in a long time, and it's certainly becoming clear that something needs to change in diabetes care so that the current system doesn't bankrupt the country. Of course, that diabetes will even be profiled in this important series confirms the extent to which the disease has moved to the front of the health care agenda.

On the continuous monitoring front, reimbursement continues to be the main barrier - we attended the CMS meeting last week in Baltimore and found the Medicare Panel not altogether there. See page 17.

Meanwhile, yesterday in New Jersey, LifeScan management gave an extremely impressive take on diabetes and its future strategy, which absolutely includes continuous – and the closed loop. We view this as a positive sign for the therapy. Never say never… we'll get there, but who said it would be easy? No one ever said that with blood glucose monitoring or pumps, and they weren't taken up immediately – the trick today is to get the right evidence, and we'll look forward to reporting back on that front as it emerges.

In the meantime – a happy autumn to you!

–Kelly L. Close

In this issue:

Quotable Quotes from September's DCU:

Dr. Robert Henry on DREAM and prevention as the future of diabetes:

- *"I think the glitazones have a great future but by no means are they a panacea. They have great potential in the prevention of diabetes, and we're going to find out more about that, of course, in the DREAM trial presentation at EASD. I predict that the DREAM results will show a significant, anywhere from 50 percent to 70 percent, reduction in the development of diabetes."*
- *"The future is good for prevention but it will require a concerted effort. The government has tried hard to push for prevention lately. It's time for pharmacologic trials that are entirely or at least partly government sponsored so that we can get studies that are robust and can tell us what kind of prevention we can expect. The DREAM trial is a first start, which will not be sufficient by itself but it will spur people to do more prevention studies. There are a lot of other studies right now too that look at other medications beyond ACE inhibitors and TZDs, but my opinion is that the most beneficial drug today for prevention is TZDs."*

Dr. Lois Jovanovic on TZDs and weight gain:

- *"People with hyperglycemia get their appetite set at a very high level, and if you bring blood sugar down and reduce glucose loss into the urine they don't have the free caloric ride they had before. Even though glycosuria decreases, the satiety center does not reset so quickly. You have*

to begin with education that when your blood sugar goes down you have to pay attention to what you're eating."

- *"I'm always looking for ways to minimize weight gain, and it would be outstanding to be able to get the benefits of TZDs without the burden of side effects. I think exenatide with TZDs is the right combination. It would be wonderful if you saw beta cells increasing in mass. These are all under review, but our opinion at this point is that this combination will be the best. My hypothesis is that since DPP-4s only protect endogenous GLP-1 from degradation and do not externally supplement GLP-1 levels, they may not increase GLP-1 enough to cause weight loss."*

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

- **August 30: MCAC meeting in Baltimore to have big time implications …**
- **August 15: Even babies are getting fatter!**
- **August 14: NYT on obesity - an infectious cause?**
- **August 13: AADE - Day Three/Four**
- **August 13: AADE - Day Two!**
- **August 11: What do you mean I can't wear my pump on the plane?**
- **August 11: The influence of money on medical science**
- **August 11: Looking for perspective on Byetta pancreatitis cases**
- **August 11: One soda a day = 15 pounds per year="That's ludicrous."**
- **August 10: AADE Day One - High-level themes**

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

1. DCU Company Watch

- **Amylin—BioCentury talk upbeat:** CEO Ginger Graham gave a brisk, optimistic presentation at BioCentury's 13th annual "Newsmakers in the Biotech Industry" conference on September 7 in New York. Most of the material reiterated information released at Amylin's Q206 earnings call, although she did lead with news on the positive Symlin / Lantus trial – we liked that, as we continue to be big fans of Symlin, even if Wall Street doesn't give a whit. Of course, Graham gave more detail on the ongoing Phase 3 trial for exenatide LAR, as this was the prime focus of analyst questions during the Q&A session. One excellent note - when asked what the predicted LAR production scale size would be, Graham said she couldn't give an answer because Byetta itself is still expanding so, well, expansively. Other topics discussed included 1) new indications for Byetta (see below) and Symlin; 2) new therapies for obesity such as PYY3-36; 3) the more potent second generation amylinomimetic (Symlin) in the works (we'll be closely watching this one as we assume if it works, it could be a boon for treating obesity); and 3) the combination therapy of pramlintide with leptin that will go into Phase 2 trials later this year (see our *DCU #58, ADA Preview, Leading with Leptin* for our June, 2006 in-depth piece on Leptin and interview with Dr. Jeffrey Friedman, the inventor of Leptin). With all the chatter about DREAM these days, an obvious question is what it means for Byetta. We do look for a positive DREAM trial, and of TZDs if that happens, but in that case, there will also likely be weight gain in most people who take TZDs, so there is an obvious place for the Byetta/TZD combo. Timing could be quite on - we look for the TZD combo indication to be approved around November, following what must have been an early January submission (the submission, which sounds like it was JIT, was announced at the JP Morgan conference early this year).

- **J&J LifeScan—Amid talk of continuous monitoring and the closed loop, LifeScan introduces aggressive new strategic goals**: J&J company group chairman and all-around powerhouse Eric Milledge gave the report for LifeScan at J&J's Medical Devices and Diagnostics Business Review on September 6. LifeScan continues to remain on top in blood glucose monitoring with 13 percent annual revenue growth over the last five years – though we note growth sure used to be easier than it is today. At the moment, the company said it holds 36 percent of the US test-strip market, ahead of Roche (26 percent), Abbott (21 percent), and Bayer (13 percent). Intriguingly, it termed Abbott as its biggest competitor – with the way it has grown in 2005-06, and with a continuous monitor not far from the market, we can see why, though we note we don't expect continuous to grab a major part of the glucose monitoring market until we see broad reimbursement, which is a ways away. Globally, LifeScan estimates a 29 percent market share, a close second behind Roche (30 percent) and ahead of Abbott (16 percent) and Bayer (14 percent). Milledge termed the OneTouch Ultra2 a major hit (see DCU #58 for our detailed report on this very cool new monitor that puts a neat focus on post-prandial tests) and from what we understand, it is surpassing sales goals left and right. We roundly applaud the Spanish-language version of the meter for the underserved Hispanic market – this is a market in dire need of focus, and LifeScan certainly seems to have provided some. Looking forward, LifeScan announced three main goals and really sort of buried the lead – it will be entering CGM! In order, the broad goals outlined included 1) In developed countries, J&J LifeScan will position itself as a comprehensive diabetes management company rather than simply a provider of blood glucose meters by including more educational resources with its products – this may sound like platitudes, but this is all about J&J's efforts to engage patients and the early results seem very strong – to boot, we just like the investment because although it costs more upfront, it's all about making patients understand what is happening and in making *them* feel they can make a difference; 2) In emerging markets, it's working with governments on reimbursement and producing meters to address patients' needs for simplicity and affordability. J&J continues to target Asia Pacific countries and has high hopes for reimbursement in Russia and China. China has, of course, huge potential with an estimated 40-plus

million people with diabetes, but only 30 percent are diagnosed and 2 percent are testing their blood glucose – unbelievable. Talk about worrying. Milledge dropped in that already the OneTouch Horizon, launched in China and India in 2004, has shipped over 850,000 systems. 3) To expand beyond SMBG, LifeScan and Animas will work to integrate insulin pump and CGM technologies into more user-friendly systems. In the pipeline: LifeScan is developing a device that will simplify testing by integrating the lancet and enzyme strip. This device will have automatic calibration and regulatory submission is expected in 2008. Bayer has been very successful with its automatic-calibration meters – although some may have asked whether it is worth it, we certainly here that this is popular – one fewer thing that can go wrong is setting the time, calibrating, etc. We also learned that LifeScan also has a newly designed meter tailored to the Japanese market, to be submitted in 2007. Traditionally, LifeScan's share in Japan has been low, and there is certainly significant upside in Japan, if LifeScan could wrest some real share from its Asian competitors. Japan is among the countries that reimburse best for strips – and LifeScan appears to be going after that with a vengeance. Also on the new product front, for pump patients, LifeScan working on an integrated meter and insulin pump where all pump functions can be controlled from the meter itself. Lastly, and extremely impressively - on the CGM front, LifeScan is developing an open-loop pump system with a disposable micro-needle transdermal sensor, which is said to require *no* user calibration and will have a warm-up time of only 3-4 minutes. Clinical trials are slated to begin in early 2007. Expect lining up for this trial…

- **Ipsen 1H06—Silence on GLP analog**: There was a bit of hand-waving but no new information on BIM 51077 during Ipsen's first half earnings report on September 6. BIM 51077 is a GLP-1 analogue Roche in-licensed from Ipsen on July 21. Ipsen CEO Jean-Luc Belingard briefly mentioned the licensing during his presentation but gave no details. At the very start of the Q&A session, Mark Tracy of Goldman Sachs jumped in with a question about Roche's upcoming diabetes day, but management gave (guess!) no information, only saying that the transfer of responsibilities to Roche has been orderly to date, and that Roche appears committed to the drug.

- **Takeda—Actos reduces stroke?!** Dr. Robert Wilcox presented findings from a new subgroup analysis of the PROactive trial at the World Congress of Cardiology on September 3. The new analysis showed that for patients with a prior history of stroke, pioglitazone reduced the risk of recurrent stroke by 47 percent. Of the 486 patients on pioglitazone with prior history of stroke, only 27 suffered a recurrent stroke, while 51 of the 498 placebo patients did. This represents an absolute risk reduction from 10.2 percent to 5.6 percent. However, there was no effect on the risk of first-time strokes. This is puzzling, and we don't think that it's a very encouraging sign. While these results are statistically significant, they would have to be replicated in a larger study to be convincing. Still, the publicity is good news for Takeda. If the DREAM results are positive as well, TZDs will really be on a high.

- **DexCom—FDA approves STS patient software; fighting words on Abbott lawsuit (and news of stay and partial dismissal):** Approval for DexCom's consumer CGM data software program was granted fairly quickly by the FDA on August 29. The software program, called the DM Consumer Data Manager, sells for $79 and began shipping this week. It allows patients to download data from the STS and view up to 30 days of readings on their personal computers (but not Macs, how drat!), including glucose trend and model-day graphs – definitely in line with how the company has been positioning CGM as a patient's tool rather than the health care provider's. Many patients have clamored for software since the STS was released – although it's true that patients can use the STS without software for quick-time corrections, it is still very tough without software to analyze basal rates, insulin sensitivity, etc. We personally were looking for information on meal-specific standard deviation, and we don't think that is available yet. In other positive news, DexCom announced August 18 that the U.S. District Court for the District of Delaware granted its motion to stay pending

reexamination of the patent infringement case by Abbott Diabetes Care. The court also struck Abbott's amendment to add three additional patents to the litigation, though Abbott has subsequently filed a separate action for these patents. Statistically, 74 percent of the patents reexamined by the United States Patent and Trademark Office between 1981 and 2004 resulted in a cancellation or narrowing of all or some of the patent's original claims. With the additional stay of reexamination, the litigation will be suspended until at least late 2007. CEO Andy Rasdal gave an aggressive statement about DexCom's commitment to further developing the STS: "*We are extremely pleased by the court's ruling as it has always been our view that Abbott's legal tactics are merely an attempt by a much larger and established company to intimidate and distract DexCom, a small company, from commercializing our STS Continuous Glucose Monitoring System, which is a new and important technology for people with diabetes*," Fightin' words…

- **Bayer 2Q06—Marching right ahead with 10 percent growth**: August 29; CEO Werner Wenning reported strong performance from Bayer diabetes care; 2Q06 sales were 213 million EUR ($272 million) up 9.8 percent from last year mostly due to strong sales of the Ascensia Contour in Europe and North America. Although this is down from first quarter, when sales growth was a whopping 24 percent, overall the sales increase of 10 percent is quite positive relative to blood glucose sales generally – as a reminder, giants J&J LifeScan and Roche reported revenue growth of 10 percent and 6 percent last quarter, respectively. Sadly, we didn't learn anything further about Bayer's diabetes business on the call, since the focus was on Bayer's Schering acquisition. There was nothing on Metrika, which we believe could grow quite well at Bayer. We did learn that Glucobay sales were 76 million EUR ($97 million), up 1 percent; this we imagine would be mostly international since the drug is not widely used in the US.

- **Medtronic—F1Q07 and sensor in NYT (all publicity is great publicity!)—Revenue up 13 percent but little said on CGM**: CFO Gary Ellis reported diabetes revenues of $196 million, up 13 percent from last year and 4 percent from last quarter. Growth was driven by worldwide pump growth of more than 20 percent -- up from mid-teens growth last quarter -- but offset by modest single digit growth in disposables (which is better than the slight decline last quarter). Trial results for comparisons of the Guardian RT CGMS against blood glucose meters will be published later this year, a definite win for Medtronic – we've been waiting for this! The STAR trials are moving along – the company is getting phase 2 started. Separately, the *New York Times* published an article by Dan Hurley on August 29 describing the author's experience going on the Paradigm Real-Time. While the assessment was definitely positive, Hurley didn't hold back on the problems he encountered: difficulty of insertion, lag time of equilibration, malfunctions, inaccuracy, false alarms, defective sensors, sensors falling out, cost, and the burden of having yet another device clipped on his belt. But the device did drastically reduce the number of hypoglycemic episodes he suffered and he's investing in the sensor now, $350 per month and all. That really says it all. While we believe the sensors still have plenty of problems, we can't imagine they won't improve in terms of hassle factor – reimbursement remains the largest hurdle. We think user and healthcare provider acceptance and even enthusiasm will follow but, as we're reminded daily by the blogs, diabetes patients are a tough crowd! Most patients remember the early blood glucose monitors (error after error…) and the early insulin pumps (so huge)… this too will improve. One big difference this time is that the payers are also a tough crowd, so we won't get anywhere on reimbursement without the evidence. Here's hoping for STAR to come through. This series of trials comparing continuous glucose monitoring and insulin pump therapy with multiple daily injections continues to progress; mgmt said Phase 1 enrollment is complete, which we believe has taken longer than would be expected. Focus groups for Phase 2 are underway, but we believe the point is to review STAR, so there probably isn't a lot going on there yet. Phase 3 is scheduled to begin in the fall. Overall we believe this trial series is moving more slowly than expected, and we will be asking about this at EASD. In the meantime, on the call, we heard that Medtronic's success with insulin pumps reflects strong acceptance of the newly approved Guardian

Real-Time Continuous Glucose Monitoring System. No metrics were given, and this seemed slightly weaker enthusiasm than last quarter, when the RT was termed the highlight of the quarter. Management mentioned during Q&A that it expects diabetes results to improve as the 'disposable issue' resolves through the rest of the calendar year. On the Guardian RT front, the sensor is expected to be available nationwide by the end of the calendar year. Last, analysts focused solely on ICD during the Q&A session – nothing about diabetes was asked. However, management did mention that diabetes was one Medtronic business that had higher-than-expected performance this quarter... and we would agree that relatively speaking, it has done well to achieve double-digit growth this quarter. Still, growth isn't as easy as it once was -- a look at the history shows that Medtronic has come from $124 mm in 2Q03 to $153 mm in 2Q04 (up 23 percent) to $178 mm in 2Q05 (up 14 percent) to $196 mm in 2Q06 (up 10 percent). If growth had been 30 percent per year as mgmt had forecast at the time of the MiniMed acquisition, today's revenue would have hovered close to $350 mm rather than under $200 mm. Food for thought.

- **Generex—RapidMist news; launch of Glucose RapidSpray:** Generex launched Glucose RapidSpray on August 10, a glucose formulation that is delivered into the mouth for more rapid absorption than glucose gels. The company plans to market to distributors for independent retail pharmacies and hopes to have the product in stores by October, 2006. We are eager to try this because, in our view, there aren't that many good solutions for hypoglycemia. (A doctor we once interviewed who has type 2 said that he takes more insulin than he needs so that his blood sugar hits a low point daily, when he can then have a Snickers bar. Although we also like chocolate, we've never been able to get the chocolate dosing right so that our blood glucose goes from 70 mg/dL to 100 mg/dL, and then no higher, all due to Scharffenberger's. To each his own …) In other Generex news, and we really file this under S for skeptical, the latest patent on Generex's RapidMist technology was granted by the Mexican Institute of Industrial Property on August 28. RapidMist is a handheld aerosol device that is used to orally deliver macromolecules for absorption through the lining of the mouth. Generex's most interesting application for RapidMist is with its Oral-lyn product, described as a rapid acting orally delivered insulin intended for people with prediabetes or type 2 diabetes. Oral-lyn is currently in clinical trials in Canada and Europe and is actually on the market in Ecuador. The RapidMist device, for what it is worth, is smaller than the Exubera inhaler and delivers insulin macromolecules for absorption through the inner lining of the mouth. Intense! It looks like this isn't an especially efficient insulin-delivery technology; we're standing aside on this one for now.

- **Biovalve morphs into Paramount and eyes the disposable pump market**: Valeritas, LLC, a new subsidiary of privately owned BioValve Technologies, announced on August 28 that it will merge with Paramount Acquisition Corp., a special purpose acquisition company. Paramount will hold majority interest in the new Valeritas, Inc., which will focus on commercializing the h-Patch Insulin Delivery System. Valeritas' main product, the h-Patch, is a daily disposable insulin pump that delivers both basal and bolus insulin. The product already has FDA approval and is in planning for Phase 4 trials prior to the expected commercial launch in 2H07. Valeritas will position h-Patch as a simple, convenient way for type 2 patients to have intensive type 1-like therapy. The device looks like it could win in simplicity of use, but we have questions about dose adjustment and – of course – the perennial cost/reimbursement issue.

- **Sanofi—Acomplia launches in Germany; fighting words on UK launch**: The Sep 1 launch makes Germany the second market to launch after Britain (June 29). Acomplia (rimonabant) is a weight management drug that Sanofi is positioning for treatment of cardiometabolic disease. Pricing is 80 euros ($103) per month's supply, or $3.66/day, roughly the same as the cost in Britain (55 pounds or $104 per month). Word is that the UK launch has been quite successful – we will be very interested to watch maintenance of those on the drug. The self-pay market depends on how well patients perceive it working and lasting and how distressing the side effects are. Xenical and Meridia, the two currently

marketed obesity drugs, have a number of GI side effects, but the global market between the two is still not so far from $1 billion - and the efficacy just isn't that great. The current European indication for Acomplia is fairly broad, as an adjunct to diet and exercise for the treatment of obese (BMI > 30) or overweight (BMI > 27) patients with diabetes or dyslipidemia. Management continues to express confidence that the drug will launch in the US by end of 2006. Acomplia would have a sizable potential market as US consumer awareness of the risks of being overweight and obesity continues to increase. Although reimbursement is important, we know some people might pay for the drug out of pocket. Our main question at the moment concerns patient drop out – remember that in trials, this was as high as 50 percent. Still, many patients will do anything to lose weight.

- **Medicis—*Science* publishes preclinical studies of ursodiol & Buphenyl for diabetes:** The August 25 issue of *Science* featured an article by Ozcan et al describing a new therapeutic pathway for treating type 2 diabetes. The authors had shown in a previous *Science* paper that obesity causes endoplasmic reticulum (ER) stress, which in turn triggers pathways that lead to insulin resistance and type 2 diabetes. Putting this knowledge into practice, they tested two drugs made by Medicis Pharmaceutical Corp. on leptin-deficient (ob/ob) mice with severe genetic obesity and type 2 diabetes. Buphenyl is currently used to treat genetic urea cycle disorders and ursodiol is used for liver and gallbladder problems. Both drugs are chemical chaperones that reduce ER stress; both restored euglycemia and reduced insulin levels in ob/ob mice but didn't affect insulin levels in lean mice. Significantly, the authors observed a small decrease in body weight (1.3 g in the lean and 4.7 g in the ob/ob mice) in the treated animals. These chaperones could potentially be an entirely novel class of type 2 diabetes drugs, which would be exciting if early clinical studies confirm the results so far.

- **Quigley Pharma—Second patent for QR-333 – vascular and neural effects**: Quigley's lead drug QR-333 was originally developed to treat diabetic neuropathy by decreasing the oxidative stress that causes the symptoms of diabetic peripheral neuropathy. It is currently in Phase 2 clinical trials for this indication. This new patent covers a new indication for QR-333 as a peripheral neural and vascular treatment drug; it was filed after Quigley researchers discovered during a proof of concept study in France that topical application of QR-333 seemed to improve peripheral circulation. Subsequent studies confirmed that the drug seems to be a vasodilator. The compound hasn't even been approved yet, of course, but the current treatments for neuropathy are so inadequate that having any approved treatment might well be beneficial to patients.

- **Lilly—Very depressing Arxxant delay at FDA- approvable letter sinks in**: Arxxant (ruboxistaurin mesylate), Lilly's retinopathy drug, received a strong negative with an approvable letter from the FDA on August 18. No word yet on whether the company will be asked to do another trial and if so, whether it will commit to the expense of a long-term study. We certainly hope there are easier, shorter questions to answer. We imagine it would be hard to convince patients to enroll in a randomized trial at this point; after the positive results from the Phase 3 study no one will want to get placebo. In that study, 10.2 percent of the non-treated group had vision loss (defined as sustained moderate vision loss), compared to only 6.1 percent of the treated group. Arxxant does, of course, have a huge potential market – apparently, over 4 million people have retinopathy, and for nearly a quarter of these (900,000) this is vision-threatening. For patients, it will be disappointing, indeed, if Lilly doesn't move forward with the drug; it's our sense that early on, the trials may not have been designed optimally, and not enough time was allowed to show the drug's efficacy. Lilly has clearly invested a great deal in the drug – to boot, it's been argued that for other complications (neuropathy etc) the company just didn't do trials that were long enough. Overall, this has been a risky submission for Lilly because it made the decision to submit only one "real" Phase 3 trial. Increasingly, the company has portrayed the Arxxant submission as two Phase 3 trials, but we believe the first one was more of a Phase 2/3.... that might be semantics or might be something that concerned the FDA. In that Phase 2/3 study, the primary endpoint (progression to proliferative retinopathy from non-proliferative

retinopathy) was missed, but they did see a significant outcome in a secondary endpoint, reduction in vision loss. Then, they changed the primary endpoint in the bigger Phase 3 study to reduction in vision loss and made progression to proliferative retinopathy from non-proliferative retinopathy a secondary endpoint. The FDA okay'd that. This, of course, is very real to patients, so that seems reasonable. (The non-proliferative to proliferative measures the severity of problems with blood vessels in the eye - nonproliferative is small damage whereas proliferative is more severe.) One wonders whether the trial just wasn't long enough to see the reduction in progression to proliferative. The "real" Phase 3 study that was submitted has been pretty convincing – so we are left waiting to see what FDA wants next.

- **TolerRx—Funding and Phase 3 plans for TRX4 monoclonal antibody for type 1**: TolerRx announced August 16 the completion of a $35.6 million financing campaign to advance research on TRX4 (ChAglyCD3), its monoclonal antibody for type 1 patients. TRX4 is an antibody against the CD3 receptor on T cells. It helps suppress autoreactive T cells and promotes T-regulatory cell activity to protect beta cells from destruction in new type 1 patients. FrontPoint Partners, LLC, was the lead investor in this round of financing; the JDRF also contributed. Other new investors included Mesirow Financial, Swiss Re, QVT Fund LP, IBT Management Corporation (IBTM), and Brookstone Capital. Existing investors that participated included Skyline Ventures, Bear Stearns, Sprout Group, Rho Ventures, Artal Services N.V., and HealthCare Ventures. The funds will go to continuing Phase 2 studies as well as a Phase 3 pivotal trial to begin later this year. Phase 2 data showed that a short course of TRX4 therapy preserved beta cell function for up to a year and a half in new patients. TolerRx is not the only developer in the type 1 prevention market. The NIH is testing Genentech's anti-CD20 cancer drug Rituxan, which is now in Phase 3 studies for new type 1's. Roche is also testing two of its immunosuppressants for new type 1's: CellCept (mycophenolate mofetil) and Zenapax (daclizumab). Also in this market is Macrogenics, currently testing CD3 Mab, an anti-CD3 antibody, for type 1 prevention. While these trials sound promising, they also sound risky – we're very impressed with the fundraising prowess for something that is still highly uncertain.

- **Amylin—Supply problems abate**: Amylin announced the end of its cartridge supply problems for Byetta on August 15, two months after it asked 40,000 physicians to stop writing new prescriptions of the drug. Increased cartridge production this summer has finally caught up enough for the company to lift its restrictions, after it added a second cartridge supplier, Baxter Pharmaceutical Solutions, to its original supplier, U.K. company Wockhardt. Amylin's sales force now plans to target 60,000 physicians to promote Byetta. Although we feel sorry that patients who may have benefited from the drug missed out for a couple of months, we suspect that this ultimately will be quite positive for demand moving forward – telling patients – and doctors – they couldn't have Byetta (if they weren't already on it) probably made those not on it want it even more. We understand that will be more, and more reps hired – Byetta is certainly hitting a sweet spot and we're glad for patients that supply issues have abated.

- **Nastech—Dose ranging trials of PYY(3-36) nasal spray for obesity to begin**: Nastech announced plans on August 14 for Phase I dose-ranging studies of PYY(3-36) in 12 subjects with BMI from 30-40. PYY(3-36) is a nasal spray formulation of Peptide YY, a hormone produced by the L-cells of the gut that seems to inhibit food intake. Nastech's technology provides a non-invasive delivery system for the peptide, which otherwise would have to be injected. The dose-ranging study will include a placebo arm and will compare nasal spray doses to intravenously administered PYY. Nastech plans to initiate a long-term safety and efficacy Phase 2 trial after determining the optimal dose for weight loss.

- **Arisaph—Second $8 million equity investment closed on new DPP-4 company in the making**: Arisaph announced August 9 the second closing of a $16 million financing round with the raising of

an additional $8 million from Kos Pharmaceuticals and Oikos Investment Partners, each of which invested $4 million. Arisaph had formed a strategic drug discovery partnership with Kos. The closing of the financing round came after Arisaph achieved key milestones including development of ARI 2243, its DPP-4 inhibitor. The funding will go in part to advancing ARI 2243 into clinical trials.

- **Merck—Mexico approves Januvia**: Merck announced August 8 it received regulatory approval in Mexico to market Januvia, making it the first country to grant regulatory approval to a DPP-4 inhibitor. Merck still expects FDA action on its NDA for Januvia to come around mid-October.

—by Jenny Jin and Kelly Close

2. A Spotlight on TZDs and DREAM with Dr. Robert Henry and Dr. Lois Jovanovic

The results of an important new prevention trial for type 2 diabetes, called DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) will be presented at EASD on September 15. Dr. Hertzel Gerstein of McMaster University Dept. of Medicine in Ontario, Canada, will be giving the presentation.

As a quick primer: the DREAM study was a large-scale, multi-center, randomized, double-blind, controlled trial intended to find if treatment with an ACE inhibitor (ramipril) and/or a thiazolidinedione (rosiglitazone) can delay or prevent the development of type 2 diabetes in people with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). The reason this trial was launched was because the Heart Outcomes Prevention Evaluation (HOPE) study showed that ramipril may delay the onset of diabetes, while the Troglitazone In Prevention Of Diabetes (TRIPOD) study showed that women given a TZD (troglitazone) after being diagnosed with gestational diabetes had a reduced rate of progression to type 2 diabetes.

All DREAM participants were randomized in a 2x2 factorial fashion in both the ramipril and rosiglitazone arms. Thus, a quarter received double placebo, a quarter received ramipril alone, a quarter received rosiglitazone alone, and a quarter received both medications. A total of 5,269 patients (4,531 IGT and 738 IFG) were recruited between July 2001 and August 2003 and followed for three years for the incidence of new-onset type 2 diabetes, other secondary outcomes, and all-cause mortality.

If the DREAM results show a significant reduction in the incidence of new-onset type 2 diabetes in patients on rosiglitazone, it would provide support for early use of TZDs in prediabetes patients. This would be very positive for sales of Avandia (GlaxoSmithKline) and Actos (Takeda). To learn more, we spoke with two leading experts, Dr. Robert Henry and Dr. Lois Jovanovic, about TZDs as a class and what they thought would come out of the DREAM study results.

Dr. Henry's background is in basic and clinical research and he is a leading proponent of the use of TZDs. In addition to being a Professor of Medicine at UC San Diego and Chief of Endocrinology at the VA Medical Center in San Diego, he is currently Chief Scientific Officer of DiObex, a clinical-stage pharmaceutical start up. He also serves on the boards of several journal publications, including *The Endocrinologist* and *Diabetes Reviews*, and is a consultant and reviewer with the NIH, ADA, VA, and with many pharmaceutical companies. He currently sits on the board of directors of the ADA.

Dr. Jovanovic is an extremely well respected clinician and researcher; in addition to numerous other awards, she has won the ADA Outstanding Physician Clinician Award in 1995, and this year was a Santa Barbara Neighborhood Clinics Health Hero. She has also received the Louis Izenstein Award for Excellence in Diabetes Care from Baystate Medical Center, Tufts University. She is the CEO and Chief Scientific Officer of Sansum Diabetes Research Institute in Santa Barbara, as well as a Clinical Professor

of Medicine at the University of Southern California-Los Angeles Medical Center. She is an associate editor of *Diabetes Care* and has served on the National Board of Directors of AACE, ACE, and ADA.

Kelly: Thank you so much, Dr. Jovanovic and Dr. Henry, for joining us to discuss TZDs – an intense topic for a late summer interview! To start off, we'd like to get your take on doctors' opinions on TZDs. It seems to us that TZDs are very popular with PCPs who don't want to get involved with syringes, glucose monitoring, and insulin dosing, but the endo community appears to be split between those who love TZDs and those who shun them. Do the two sides speak the same language?

Dr. Jovanovic: Bob, you are really the pioneer in this field, so I'll let you take the lead here.

Dr. Henry: Well, let me take a try at this. To start off, I'd stress that TZDs are a unique class of compounds that offer benefits that cannot be achieved with other medications at this stage. They do have a certain element of concern, but for the most part they are *reasonably* safe. They are unique in their mechanism of action and thus, in how they benefit type 2 patients – the bulk of their effects come from indirect as well as direct mechanisms of action. First, they act on adipose tissue to increase adiponectin and redistribute fat to the subcutaneous regions, which may be the major mechanism by which they decrease insulin resistance and increase insulin secretion. Second, remember that they also act on fat metabolism by regulating a large number of fatty acid genes that have been implicated in insulin resistance. To date there is nothing else that offers what they do. You can say that metformin also improves liver insulin resistance but its effects on peripheral tissues are modest and it acts by a mechanism that is not well delineated and certainly different from TZDs.

Kelly: There's been some serious speculation that TZDs *may* also have the potential of preserving beta cells. What do we know about that today?

Dr. Henry: In his TRIPOD study, Tom Buchanan showed a reduction in the development of type 2 diabetes in females at high risk because of a past history of gestational diabetes. This was a beautiful study showing that decreasing the stress on beta cells in these high-risk individuals decreased their risk of developing diabetes. This also brings up the point that TZDs are probably more efficacious if given in the early stages of diabetes, including in the prediabetes phase. A lot of short-term studies have shown improvement with glitazones in the development of impaired glucose tolerance (IGT) and diabetes, including the Diabetes Prevention Program (DPP) study. In a 10-month period DPP patients on troglitazone had a 75 percent reduction in the development of diabetes. (Ed. note – in this study, Rezulin (troglitazone) was used, and it was removed as a study drug in DPP some time earlier than it was removed from the market, due to liver toxicity, arguably making this finding all the more striking, due to the short time period.) This result is not too different from what Buchanan saw in the TRIPOD study. Glitazones also have pleiotropic benefits. They act as anti-inflammatory agents, though their effect on tissue inflammation may also be secondary to the redistribution of fat away from ectopic sites, like liver and skeletal muscle. They enhance fat oxidation in ectopic sites, which is beneficial because ectopic fat is likely involved in inflammation and is associated with hepatosteatosis. TZDs also act on a number of CVD risk factors, either directly through effects on the vasculature and endothelium or indirectly though effects mediated on adipokines, interleukins, TNF-α, and other cytokines. Now, I don't know if their cardiovascular risk factor benefits translate to reduced CVD outcomes. The PROactive study did not achieve statistical benefits on the primary composite end-point but it did

shed a lot of light on the benefits of pioglitazone in type 2 diabetes patients with a history of previous cardiovascular disease. There certainly were a number of significant metabolic benefits. I feel that they probably studied people too far down the road in terms of cardiovascular disease progression, with little likelihood of reversibility. I'm a little concerned about whether the large scale long-term trials that are necessary to study cardiovascular prevention in people earlier on in the development process of type 2 diabetes will now happen because pioglitazone will be generic early in the next decade, and such studies require five years or more for completion

Kelly: Certainly, there would be less incentive to do those studies with patent expirations coming up. Wow, so it sounds like you're pretty strongly in favor of this class on the whole.

Dr. Henry: I think the glitazones have a great future but by no means are they a panacea. They have great potential in the prevention of diabetes, and we're going to find out more about that, of course, in the DREAM trial presentation at EASD. I predict that the DREAM results will show a significant, anywhere from 50 percent to 70 percent, reduction in the development of diabetes in this high-risk population. Ramipril added to the glitazones may have an additional benefit. You're right – I think this is a pretty strong endorsement of TZDs. I also feel that they are best in combination therapy, especially with metformin, because of the weight gain that is caused by the change in fat deposit patterns. The combination of metformin with TZDs tends to minimize weight gain, yet have additive glycemic benefits. A downside on glitazones is their propensity for weight gain. This is why physicians must make a major effort when they prescribe these medications to make sure patients understand they'll gain weight if they continue on their current diets. Caloric intake should be scaled back.

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Jim: We've read a lot about other side effects – which other ones concern you?

Dr. Henry: Another one is the occasional development of peripheral edema. The mechanism remains to be determined but may, in part, be mediated by TZD effects on PPAR-γ receptors in the collecting ducts of the kidney. People do get edema, although not frequently, and it is sometimes associated with increases in CVD risk. In a recent 52-week-study with rosiglitazone, patients with class 1 and 2 heart failure had a higher risk of heart failure and cardiac events when treated with rosiglitazone. That is one reason I prefer early treatment with these compounds: I believe there will be fewer cardiac side effects for patients in the early stages of diabetes because they don't have as many cardiac complications as they have after a decade or more with the disease.

Kelly: I hadn't realized the correlation between early treatment and fewer side effects – do you think that is widely known?

Dr. Henry: I don't believe this has been addressed in clinical studies, but overt cardiac disease increases as the duration of diabetes increases. It seems that individuals with a history of pre-existing cardiac disease including congestive heart failure are at greater risk of cardiac decompensation. Since these cardiac complications are less frequent in type 2 diabetes patients of recent onset, it is likely that glitazones may be better tolerated from the cardiac standpoint when used earlier on in the disease process.

Jim: Dr. Jovanovic, let's turn to you. Please talk to us about your experience and concerns about TZDs.

Dr. Jovanovic: Bob has kindly done all the positive sides and then flipped a little bit into negatives. A couple of things that should be emphasized are the very early use of these drugs and actually using them in *prevention*. Tom Buchanan's TRIPOD is my favorite study, which included women with *previous* gestational diabetes; of course, you can't give them these drugs during pregnancy – so to be clear, they didn't have diabetes *yet* and that, of course, is what was being tested. They had normal blood sugars, but the incidence rate of type 2 diabetes is 10 percent per year for women who have had gestational diabetes, so you would predict that 50 percent would have diabetes after five years. And in this study their population actually had a risk of 12 percent per year, as this was a high-risk population. *And* they saw a 60 percent decrease from the expected prevalence after just 3 years with troglitazone, which is amazing. This decreased rate was sustained beyond the time that troglitazone was taken off market and the study stopped.

Jim: What do you believe accounted for that decrease in incidence?

Dr. Jovanovic: If you give TZDs early, you get a downward slope of diabetes incidence by reducing the burden on beta cells. You can actually make a difference in the destiny of someone destined to get type 2 diabetes. If you look at TZDs for women with polycystic ovarian syndrome (PCOS), their blood sugars are not high yet, and in those trials the women didn't gain weight. We were not allowed to continue that study so we still use metformin for PCOS now, but the study showed that if you start early use of TZDs before hyperglycemia, the weight gain doesn't occur.

Kelly: What *does* cause the weight gain?

Dr. Jovanovic: It may be that weight gain is only associated with normalizing high blood sugar in someone who doesn't change their behavior. I have 4,000 diabetes patients in my Santa Barbara clinic. In our clinic if you use TZDs in patients with frank type 2, these are patients at high risk of gaining weight and at increased risk for edema. They're usually women, obese women, those with the highest blood sugars. In fact, if you were to identify a patient population you really didn't want to get weight gain and edema, it would be *precisely* these patients with high CVD risk who are already overweight or obese. It doesn't mean they won't show remarkable A1c improvements on TZDs, but in my county clinic, 15 percent of the women with diabetes have significant weight gain on TZDs, which means more than 5 kg. Even though their blood sugars are better, this may not be the right direction of prescribing therapy. I think, Bob, that we're saying the exact same thing. But we need to talk about who can gain the most from TZDs with the least risk.

Dr. Henry: I concur. And it has been shown in clinical trials that females gain more weight than men on TZDs. Whether there is a reason for this is not clear. But even before troglitazone was approved, almost a decade ago, it was known that females gained more weight with these compounds.

Kelly: Could you say a word about the optimal population for TZDs?

Dr. Henry: As I stated earlier, I feel that the TZDs may prove to be optimal therapy early in the development of type 2 diabetes; this is where they are usually most effective. Insulin resistance is often very severe and insulin secretion, while not normal, is still adequate if insulin resistance is reduced sufficiently. Probably the best time to use TZDs, in terms of

preventative potential, is before they develop diabetes but are at high risk (for example, if they have impaired glucose tolerance). Such prevention has not been approved by the FDA, but the short studies done to date have been compelling. The results of the DREAM study will go a long way to cementing this concept. Perhaps one of the mechanisms leading to prevention of diabetes is that TZDs, either by direct or indirect effects, may be able to alter the natural decline in beta-cell function that invariably occurs in type 2 diabetes. Studies are currently underway to examine whether the potential for beta-cell sparing occurs with early TZD use.

Kelly: Could you share your views about whether the potential beta cell benefits outweigh the CVD risks?

Dr. Henry: The CVD benefits and risks are pretty clear with TZDs– the potential anti-inflammatory and vascular benefits usually offset small increases in fluid retention in most patients, but when those increases are excessive in a patient with compromise cardiac function it may increase the risk of congestive heart failure. There is a balancing in such patients of benefits versus risk. One needs to be really cautious in the use of these agents in people with a history of overt heart failure, even when stable, but I think that when TZDs are used carefully and cautiously the benefits usually quite significantly outweigh the risks. While there are patients where one needs to carefully consider the risks, overall the benefits are pretty apparent.

Kelly: The earlier literature focused on TZD 'responders' and 'nonresponders.' Is that distinction still relevant? Is weight gain linked to response?

Dr. Henry: You don't need to gain weight to get the benefits, although fat redistribution to subcutaneous depots is an integral mechanism of the TZDs, and some weight gain will usually occur unless calories are cut back and/or energy expenditure is increased. In a situation in which you don't provide support for the prevention of weight gain, people do tend to gain weight as Lois said, and it has been noted that not infrequently people who gain the most tend to get the most glycemic benefits, but this is probably because the mechanism of action is to alter fat storage and function.

Dr. Jovanovic: We saw the same thing with DCCT: when people with terrible control get under good control they tend to gain the most weight. People with hyperglycemia get their appetite set at a very high level, and if you bring blood sugar down and reduce glucose loss into the urine they don't have the free caloric ride they had before. Even though glycosuria decreases, the satiety center does not reset so quickly. You have to begin with education that when your blood sugar goes down you have to pay attention to what you're eating. Even without TZDs you will gain weight. You have to work on what patients will call caloric restriction. You have to carefully prescribe caloric restriction when you restrain glycosuria or patients will continue to feed themselves to satiety and gain weight.

Jim: Aside from weight issues, are there other reservations that strike you?

Dr. Jovanovic: In Tom Buchanan's study it was gestational diabetes, and some of those women became pregnant again. I'm worried about women in childbearing years getting pregnant on these drugs. However, the pharmaceutical company Parke-Davis had a registry, and they found no increased risk in pregnancy complications with women on TZDs. We know that metformin prescribed for PCOS can be used into the first trimester because there is are so

much safety data, but the same is not yet true of TZDs. It would take 500 exposed pregnancies to prove the null hypothesis: that TZD's do not cause malformations.

Kelly: The Byetta TZD combo was submitted to the FDA, we believe, in early 2006, so we would assume a decision will be coming soon. Assuming it is approved, in terms of combination therapy, do you think Byetta plus TZDs will be the best of both worlds? Patients get fasting control from TZDs and postprandial control from Byetta by complementary mechanisms. Plus, no weight gain. Would you be more willing to combine TZDs with Byetta or with DPP-4 inhibitors?

Dr. Henry: DPP-4 inhibitors are still under review by the FDA. But I think that TZDs and Byetta could be an ideal combination because, as you point out, exenatide and glitazones have complementary mechanisms of action, and Byetta will likely minimize or prevent any weight gain with TZDs. There's a good chance that TZDs with GLP-1 analogs could be extremely potent in lowering blood sugar without any significant hypoglycemia. That doesn't mean that patients can't get hypoglycemia, but it will be relatively uncommon with that combination. I think it's a great potential combination – I have seen some data, and it looks very impressive, but the FDA will rule on that ultimately.

Jim: Does combination therapy have any other benefits?

Dr. Henry: I think so. The future for diabetes is in prevention, and that generally requires some beta cell preservation or regeneration, and the GLP-1 analogs like Byetta have at least in animal models shown evidence of beta cell preservation and perhaps at higher levels beta cell regeneration. There is the possibility of added benefits when we put GLP-1 analogs with TZDs, which also show beta cell preservation in animal models. This is pure conjecture, but it is something that needs to be addressed in clinical trials if this combination is approved by the FDA. I think Byetta and TZDs represent a very attractive combination. It would require injections twice a day of Byetta and one or two a day oral glitazones. But with GLP-1 analogs, of course, there is a lot of interest in a long-acting formulation, which may be given only once a week. I'm very enthusiastic that this new combination (exenatide and TZDs) will be approved and used.

Dr. Jovanovic: Of my 4,000 patients I'm probably overemphasizing the ones that require the most time. I'm always looking for ways to minimize weight gain, and it would be outstanding to be able to get the benefits of TZDs without the burden of side effects. I think exenatide with TZDs is the right combination. It would be wonderful if you saw beta cells increasing in mass. This is an exciting forefront for us to begin looking into. These are all under review, but our opinion at this point is that this combination will be the best. My hypothesis is that since DPP-4s only protect endogenous GLP-1 from degradation and do not externally supplement GLP-1 levels, they may not increase GLP-1 enough to cause weight loss. In preliminary studies they were not associated with significant weight loss whereas the Byetta studies are so exciting because you see that therapy *is* associated with weight loss. My hypothesis is that the weight loss you see with Byetta and TZDs can't be extrapolated to DPP-4s.

Dr. Henry: I agree. GLP-1 augmentation with DPPs is much lower than is possible with GLP-1 mimetics like exenatide, and I think GLP-1 is a major contributor to weight loss. That's probably why DPP-4s won't result in significant weight loss.

Kelly: Dr. Henry, you mentioned that you believe that DREAM will be a pretty positive trial. What are the implications? To what extent will this support use of TZDs in prediabetes?

Dr. Henry: Yes, absolutely, my feeling on DREAM is that it will be positive. The question is how positive. It has to be at least a 50 percent reduction in risk to make a big splash. I'm hoping it will be 50 percent or more; I'm certainly hoping it's not less. The implications are – well, most people realize diabetes prevention is the future. It has to be with our current unmanageable and unsustainable incidence rates of diabetes. The number of new cases per year is just astounding. But the difficulty with prevention studies is the question of who is going to carry the ball? Who is going to go for registration of a glitazone when there isn't much time left on patent life for pioglitazone? That makes it not very attractive for rosiglitazone as well. I don't think the DREAM trial will be enough for FDA registration. I don't know that for sure, but the FDA would have to be approached and GlaxoSmithKline may do that, but it may require more extensive testing. It would be a great first step if one of the companies would apply for registration if the results are strongly positive, but it would require some restriction by the FDA on the people who qualify. We'd have to start with those at the highest risk. A lot of people would like to prevent the metabolic syndrome, which is not infrequently associated with pre-diabetes (IGT and IFT). The number of Americans with pre-diabetes is very high – but it has not been studied well enough for TZDs to be used as a preventative therapy quite yet.

Jim: Given that problem, are you still optimistic about TZDs getting approval for a prevention indication?

Dr. Henry: The future is good for prevention but it will require a concerted effort. The government has tried hard to push for prevention lately. It's time for pharmacologic trials that are entirely or at least partly government sponsored so that we can get studies that are robust and can tell us what kind of prevention we can expect. The DREAM trial is a first start, which will not be sufficient by itself but it will spur people to do more prevention studies. There are a lot of other studies right now that are looking at other medications beyond ACE inhibitors and TZDs, but my opinion is that the most beneficial drug today for prevention is TZDs.

Dr. Jovanovic: I have to confess that my only knowledge of DREAM is what has been published so far. However, I thought that the rationale behind the study design was very interesting – the trial came almost by accident out of the HOPE trial, in which they noticed there was a reduced prevalence of type 2 diabetes in patients on glitazones. It's interesting that there was a launch of such a huge trial based only on the preliminary data of a previous trial. It's very exciting that the world is so excited about diabetes prevention that they would put funding into something like this. I wouldn't be surprised if this launched more studies and other funding. But this is entirely a Canadian group – it is not international or American. I don't know if this makes a difference in politics – Bob is probably right that there will be positive results – but before any indication for prevention it will have to be enlarged in the US. I don't know if this is always the case, but I would imagine the FDA would like a US study before they go that far.

Jim: Dr. Jovanovic, if DREAM is positive would you use TZDs as first line therapy?

Dr. Jovanovic: My hypothesis is that if they are used before hyperglycemia, they don't cause weight gain. So that is not my issue in terms of using them as prevention drugs.

Jim: Why are you more reluctant to use TZDs than other clinicians?

Dr. Jovanovic: I think it's worse for me because I feel responsible and guilty for the weight gain in my patients. They will actually prefer it because they know the alternative is injections. More often, I'm stopping the therapy, not them. They don't want injections.

Kelly: Would they have the same problem with Byetta since that is also injected? Would you use DPP-4s if they were approved?

Dr. Jovanovic: I can't answer that yet. But I can tell you that certainly insulin comes with a lot of crying in my clinic.

Dr. Henry: Insulin is problematic for us too. We do start a lot of people on it but not without a lot of work on our part. But it's much easier to go on Byetta than insulin because it's not fraught with the same problems like the potential for severe hypoglycemia.

Jim: Bob, you think the future of type 2 diabetes is prevention. What do you think the future of type 1 diabetes is?

Dr. Henry: The same thing, but I'm not an expert in type 1. I do think there is some terrific work going on in that field. It's a tough nut to crack because of the underlying autoimmune disease, but I think it's still like type 2 in that prevention is where the future is. We know how to prevent or delay type 2 diabetes more effectively, but saying that and actually making it happen are quite different issues. Just because we know how we might prevent the development of type 2 doesn't mean we can get people to adhere to those regimens. In type 1 my hope is that with recent developments we're well on our way to starting to crack the nut. It may take another decade or two, but we're starting to see significant advances that we never saw in the last couple of decades, when we had a lot of hoopla but no results. I'm hopeful that's going to change.

Dr. Jovanovic: Bob, you say it for the both of us.

Kelly: Thank you both so incredibly for sharing time with us today – it's been an honor and a privilege spending time with you both.

--James S. Hirsch and Kelly Close

3. Continuous monitoring and reimbursement: harsh assessment of CMS MCAC meeting

We attended the Medicare Coverage Advisory Committee (MCAC) on August 30 in Baltimore. Unfortunately, we felt like we had walked back in time about, oh, a quarter century.

The committee did not make any decisions that will immediately undercut diabetes patients or the companies that sell goods or services to them. But several comments from Medicare panelists raised doubts about the need for one of the most important tools in diabetes management: home glucose monitoring. Frankly, we thought these battles had been won long ago; while some patients need to test more often than others, all patients (type 1, type 2, gestational, children, elderly, etc.) need to monitor their blood sugars on a regular basis to maintain tight glycemic control.

It appears, however, that this memo has not reached some Medicare officials. Never mind that the DCCT (completed in 1993), plus dozens of other studies since, have provided overwhelming evidence that near-normal blood sugars reduce the risk of complications. These studies, ending the long debate over the

importance of good control, made blood testing an essential part of diabetes care. But inexplicably, some panel members believed the value of testing, particularly for type 2 patients, was "inconclusive," while other panelists seemed simply confused by the matter. In many cases, the thrust of the naysayers' dissent was this: testing is often wasteful because patients don't know what to do with the numbers. Talk about irony! Patients often don't know what to do with their numbers because they haven't been educated, but they haven't been educated because payers – including Medicare – woefully underfund education (e.g., by not funding diabetes educators, by refusing to pay for email correspondence, phone calls – the list goes on and on.)

At any rate, the panelists' comments don't bode well for future reimbursement decisions related to testing and highlight how difficult coverage will be for the far more expensive continuous monitoring technology.

Medicare, of course, wields enormous influence in determining what medical products and services get covered, and by how much. Its reimbursement decisions not only affect millions of patients directly but guide private payers as well.

In 2003, Medicare spent just under $1 billion on testing. According to the Medicare website, this benefit is available to all Medicare recipients with a 20 percent co-pay for testing supplies after a specified deductible with no apparent strip, lancet, or monitor limit.

MCAC specifically met in August to review evidence regarding glycemic control among Medicare patients and the role that testing – both continuous and conventional – can play to improve outcomes for type 1 and 2 patients, particularly those 65 or over. The meeting was unusual in that no decision on coverage was ever considered. Rather, the goal was to identify both current and needed research on the matter. We were encouraged by the medical luminaries who spoke in favor of testing (Dr. Howard Wolpert, Dr. Steve Edelman, and Dr. Irl Hirsch, among others), but their advocacy only underscored the gap between the clinicians who want to improve patient care and the bureaucrats who are trying to hold down costs.

We don't believe, based on this meeting, that anyone in the diabetes community should panic – no one proposed that Medicare reduce current coverage of test strips – but a warning signal has been sounded.

Based on what we heard, we believe that CMS is far from making any coverage decisions. The cry is for more data, more data, more data. The day's agenda included a panel vote on questions to determine whether evidence exists that more frequent testing and better glycemic control improve outcomes for diabetic patients over the age of 65. We found the wording and tone of the questions challenging, and we were disappointed that the typical response for almost every question was "uncertain" or "very uncertain." Remarkably, the panelists told us in their voting that they aren't certain that glycemic control and testing really matter for type 2 diabetics. And, with respect to continuous monitoring, they would need to see evidence related to A1C changes, hypoglycemia rates, and hypoglycemia-related falls to determine CGM's value.

In the post-vote discussion**,** Dr. Steven Phurrough, head of CMS coverage decisions, implored industry to figure out what the right metrics are for evaluating continuous glucose testing before a coverage decision is requested. He asked what the relevant measurements are – number of glucose excursions? Percent of scores in or out of a specified range? Percent of time spent at risk? He charged CGM (and SMBG) advocates (namely, industry and JDRF) with figuring out the right questions to ask and answer. While we agree that industry, JDRF, and thought leaders have a real opportunity to shape the argument, we remain puzzled that the value of better glycemic control – and the tools that facilitate it – could come under fire.

We were frankly shocked that smart people cannot agree on what the existing data say – regardless of the age of patients – even when the data come from well-respected sources. While we agree that "more testing leads to better care," we were surprised that some of the speakers could conclude that the value of testing is, well, "inconclusive" at best. Most notable was Dr. Elizabeth Koller, lead medical officer for CMS, who inexplicably took some shots at the DCCT and questioned its validity for older type 2 diabetics. (Later, one audience member in the Q&A expressed disbelief that experts questioned the DCCT. He described it as "a first".) Dr. Koller also seemed to argue that treating older patients has less value that treating younger ones. She offered a statistic (data source unknown) that 84 percent of the treatment benefit came from treating 17 percent of the youngest patients with the most control problems. She was suggesting (we think) that older people have bigger problems than diabetes, so it makes more sense to treat younger patients with the disease. She also said that glucose monitoring doesn't seem to lead to prolonged life or less CVD (what was the EDIC study again, we wondered?); and glucose control doesn't seem to be as much of a factor in reducing complications as treating hypertension or lipid problems. We were stunned at some of these assertions, particularly the first one, and we were busy investigating the source until we gave up.

Regarding cost, another Medicare representative alluded to the expense of excessive type 2 testing. Dr. Art Lurvey focused on the costs of testing to Medicare – just under $1b in 2003 – and it was pointed out that 60 percent of patients with diabetes on Medicare are not on insulin. He argued that there is too much testing for "stable" type 2 diabetics because testing rarely leads to changes in therapy. Stable?! Who said anything about stable? We found the implication comical, when the literature bristles with studies about patients who aren't on insulin and are anything but stable. Lurvey also described testing by older institutionalized or home patients as wasteful – he said these patients are tested repeatedly by nurses who do nothing with the information. Again, it's hard to believe that this is a major problem. As well, he criticized heavy marketing campaigns to patients who don't understand how to use the information they collect. Please. We think educational programs are doing better and better at engaging patients, and if patients aren't going to learn through industry, where else will they learn, given that so few (well under a third) see diabetes educators and that doctors' time with patients has become so limited. We would argue that with nearly two thirds of patients with diabetes not at goal (A1c <7), *more*, not less, testing is needed as well as more education and direction as to what patients should do with the numbers. That said, when patients receive more education, they may well wind up looking to use more tests (for post-meal testing, for example), not fewer – and if that makes them healthier over the long run, CMS should stand up and applaud.

So, one piece of good news: most seemed to agree that ACCORD is likely to answer many questions about the value of testing; the bad news is that some think that any coverage decisions should be postponed until the data are out in 2010. Panel member Dr. Harry Burke (Associate Professor of Medicine, George Washington University Medical School) in particular noted that waiting might be worth it.

The best, most reasonable presentations reinforced the emphasis on patients. Dr. Irl Hirsch (U. of Washington), Dr. Steve Edelman (UCSD), Dr. Aaron Kowalski (JDRF), Dr. Kevin Peterson (American Academy of Family Physicians), Dr. Howard Wolpert (Joslin Clinic), and Dr. Richard Bergenstal (International Diabetes Center) all made cogent presentations demonstrating that more testing helps get A1Cs closer to "normal" and that the closer to "normal" a patient gets, the better they do. Testing is a key component of safe diabetes management. Peterson noted that we are in an age of evidence-based medicine with many primary doctors being evaluated on bringing down A1Cs, and glucose testing is critical to achieving that goal. From this group we heard strong, rational arguments that glucose control is key to lowering microvascular complications (as noted, EDIC also proved reduced macrovascular complications in type 1 patients); testing is important to lowering A1Cs safely and testing regimens need to be tailored to the patient over time. We heard passionate arguments from this group –

from nurse educator Paula Yutzy in particular. She pointed out that over a decade ago she fought to get testing coverage mandated, and now her Medicare patients are the only ones who are able to consistently pay for supplies – with excellent results. She lambasted CMS for the troubling tone of its questions but expressed hope that it was still possible to optimize and improve current care and coverage.

Back on the negative side, we also heard very negative comments from the panel. In particular, Dr. Rodney Hayward (guest panel expert, Director of VA Ann Arbor Health Services), suggested that the logic of 'more data is better' is frequently a fallacy. In fact, he argued that often, more data does harm, not good. We disagree, but we'd also emphasize that teaching patients to use the data is a must-have, not a nice-to-have. He also implored CMS not to base a coverage decision on intermediate outcomes. He argued that supporters should do the studies and prove the benefit rather than expect acceptance based on anecdotal experiences. The most confusing – and we think strange – worry on the part of a panel member came from Dr. Mark Fendrick (University of Michigan), who argued that all the press on more testing is likely to create a testing free-for-all in which patients test so much that they increase hypoglycemic events.

We, um, disagree.

So what does all of this mean for patients? On the one hand, nothing happened and nothing changed with respect to Medicare coverage. However, we do not like the veiled threat posed to the importance of glycemic control – and the testing required to achieve it – by even having this meeting. We wonder if some of the panelists have an eye toward carving out Medicare groups that get lots of tests reimbursed – and groups that get far fewer tests reimbursed. Unfortunately, non-Medicare payers frequently use Medicare decisions as a reason to reimburse less.

And what about the companies with testing technology – continuous and conventional? Again, as with patients, no really bad news came out of this meeting. But no really good news either, particularly with respect to more reimbursement for technology like continuous monitoring. (Don't forget, we had one panel member suggesting a delay of any coverage decision until 2010 when ACCORD data are available!) This meeting bolstered our thesis that reimbursement is hard to get in diabetes but crucial for mass adoption. For the companies with continuous monitoring technology (Dexcom, Abbott, Medtronic) we continue to expect evolution, not revolution, in adoption. Revolution would only come with widespread, healthy reimbursement. Our concern for conventional monitoring companies (JNJ, Roche, Bayer, Abbott, BD) is that Medicare (and others that will follow) might attempt to segment its patients and limit the number of tests it will reimburse by some arbitrary standard that helps the bottom line but hurts patients. Clearly any move in this direction hurts the testing franchises (conventional and continuous) of all of the above companies.

—by Cindy Glass and Kelly Close

4. AADE Update: Highlights abound!

This year's AADE meeting took place from August 9-12 in sunny Los Angeles, California. Close Concerns sent a big team to cover the conference, which gave us the opportunity to not only attend many sessions, but to also survey nearly 150 diabetes educators about current trends in leading diabetes therapies and devices such as Byetta, DPP-4 inhibitors, inhaled insulin, and continuous glucose monitoring (we'll share our survey results next issue). From the exhibit hall floor to the conference rooms, our team was busy taking notes and taking advantage of the unique clinician perspectives that both presenters and attendees at the AADE have to offer. In general, the corporate-sponsored symposia on the first day of the conference were excellent. The quality of the breakout sessions ranged more across the spectrum. Below we present the highlights.

- **Byetta is huge**. Predictions are high though current use still remains relatively low. Our team heard the Byetta chorus again and again from the CDEs at this conference. According to our own survey, though the vast majority of educators still have well below 10 percent of their patients on Byetta, on average educators think about 42 percent of type 2 patients would benefit from the product. Forty-two percent! We knew Byetta had lots of upside, but we were still surprised by its support from CDEs. But as we got into more in-depth conversations, we realized that the CDEs are eager for label expansion – combination therapy has always been important for educators, but they've not had a good agent with which to combine. Now there is high interest in combining TZDs and insulin with Byetta, and also Byetta in monotherapy. Although CDEs may recommend off-label use, we don't have the impression that PCPs are always comfortable with it, nor even endos, so real label expansion definitely matters. Disappointingly, the almost palpable attendee enthusiasm for Byetta did not translate to conference content; many presenters mentioned Byetta in their talks but there were no specific sessions on Byetta beyond Amylin's symposium and product theatre. Nonetheless, we hope (and expect) that what we learned in our survey will translate into explosive growth for Byetta, which has now been on the market for two years.
- **DPP-4 inhibitors lack potency but have promise**. Educators are reserving judgment, but are eager for another alternative. Most seemed unimpressed with the potency of compounds at FDA currently – Novartis' Galvus, and Merck's Januvia – but felt that they would have some use, likely mostly by PCPs.
- **Symlin is wildly underused**. It was striking to us the extent to which educators discussed how underused Symlin is. Whereas Symlin's benefits do not seem wholly understood or accepted by endocrinologists (to say nothing of primary care doctors), they do appear to be well understood by many educators. As well, there was a great deal of buzz about pumping Symlin, and while we think the absence of reimbursement will make this difficult for many patients, we did speak to one educator that had a trial using Symlin in a pump – we thought that was pretty interesting. We have personal (very good) experience with this and believe it will ultimately be viewed as "more physiologic" and therefore better. But there is a high cost and high hassle factor to pumping Symlin. We believe Symlin pens will help create a "poor man's" Symlin pump and that Symlin will be more appealing to patients once it is in pen form. On the obesity front, interest was also high – we have the impression that a number of educators already take Symlin off-label. We expect we would be hearing sometime soon that Symlin is moving into Phase 3 trials.
- **Reimbursement tensions have risen versus a year ago**, especially with little to no coverage for CGM. Major questions on reimbursement also surround inhaled insulin and DPP-4 inhibitors, to say nothing of time spent by educators. No good solutions prevail and educators overall seem quite pessimistic on this front.
- **Continuous glucose monitoring** – not ready for prime time, though interest is very high. A surprising trend we picked up was the near disdain for CGM by educators who have many patients who simply cannot afford the technology. Pessimism about reimbursement was rampant – 90 percent of educators chose 2008 or 2009 when we asked them which year from 2006-9 they expected reimbursement would arrive. A few said "never!" On the flip side, the technology itself is viewed as at least somewhat efficacious, and many educators want to use it—but they're frustrated by the absence of reimbursement and questions related to accuracy, reliability and timing problems. That said, Medtronic's symposium was a win for them – it featured very positive talks by Francine Kaufman and Allison Wick. Gary Scheiner's session on retrospective CGM data analysis was also enthusiastically received. But, to keep things in perspective, 92 percent of audience members at the Medtronic symposium said that fewer than 10 percent of their patients use CGM, and almost all the CDEs at Scheiner's talk felt they were undertrained on how to analyze CGM data.
- **Lots of interest was shown in earlier, more aggressive therapy**, which is starting to happen more with Byetta. Many sessions focused on earlier self-care, rethinking the chronic care model, and overcoming insulin resistance. Seventeen percent of CDEs we surveyed thought AADE7, or the chronic care model, was the most notable trend of this conference. The AADE7 are seven behaviors

that serve patients well – healthy eating, being active, monitoring, taking medication, problem solving, healthy coping, and reducing risk. Although these may sound straightforward, the AADE has been focused on how to make patients take responsibility for these behaviors; based on current stats, it seems they have a ways to go. Industry obviously continues to be very interested in pushing this theme forward. Pfizer, Lilly, and Sanofi-Aventis sponsored symposia on better glycemic control and/or on overcoming insulin resistance. While corporate symposia have stressed these themes for years, we saw them more than ever before in the breakout sessions on prevention, patient education and self care, and treatment.

- **Interest in inhaled is higher than expected**, with opinions raging widely. Pfizer's booth was the busiest in the entire exhibit hall, featuring demonstrations of the inhaler and a video of a physician explaining its use. Ginger Kanzer-Lewis gave a detailed talk on Exubera at Pfizer's product theater, where CDEs murmured about exclusion criteria, dosing, and inconvenience. In our survey, inhaled did not generate significant safety concerns, but it did produce a wide range of opinions; and we heard vehement criticism as well as enthusiasm for the product. Every time inhaled came up in a question-and-answer session, tension hung in the air as everyone craned to listen for the presenter's opinion—official opinions were generally conservative.
- **Primary prevention** – greater prevalence means we need better strategies (and more money). Statistics about prevalence were an obligatory introduction to every session, particularly the sessions that argued for prevention. These included Dr. Edward Wagner's general session address and Dr. Pamela Allweiss' presentation of an encouraging pilot program for occupational prevention by GE Energy. Lack of reimbursement for prevention programs was a recurring theme, and recalcitrant hospital administrators cutting prevention funding was an oft-heard complaint.
- **Still a long way to go with inpatient hyperglycemia**. Not surprisingly, this is an audience eager for more movement on the inpatient, tight-glycemic control front but we didn't hear a whole lot new here – it's the same old thing – the evidence is overwhelmingly in favor of tighter glycemic control, but the hospital system remains fragmented and under budgetary fire – so unless regulatory body JCAHO steps in, it will be unlikely to see much change on this front.
- **Complications are significantly undermanaged**. Beverly Dyck Thomassian's presentation on the dangerous and often under detected comorbities of diabetes was a sobering reminder of the need for multi-faceted care. Virginia Valentine's talk on diabetic neuropathy also reiterated the lack of adequate specialist care and new therapeutics for neuropathy. We heard many opine that prevention is the most important new trend in diabetes; but obviously many patients who have acute complications are seen by providers who don't treat the underlying disease optimally – or, some would say, at all.

—by Jenny Jin, Dan Belkin, Cindy Glass, Nupur Lala, Patty Pringle, and Kelly Close

5. On Symlin: Compelling Consensus Development Conference on Pramlintide in the Management of Type 1 & 2 Diabetes

As most DCU readers know, pramlintide (Symlin) was approved by the FDA in March 2005 as an adjunct treatment in patients with type 1 or type 2 diabetes who use mealtime insulin and who have failed to achieve desired glucose control, despite optimal insulin therapy. Pramlintide is a synthetic analogue of amylin, a neuroendocrine hormone that is co-secreted with insulin from pancreatic β-cells. Amylin complements the actions of insulin by suppressing postprandial glucagon, slowing gastric emptying, and inducing postprandial satiety in direct proportion to food intake, thereby coordinating the rate of glucose appearance in the circulation with the rate of insulin-mediated disappearance of blood glucose. Anecdotal evidence indicates that pramlintide also confers a greater sense of well-being and energy, referred to as the feel-good effect.

Like insulin, amylin is absolutely deficient in patients with type 1 diabetes and relatively deficient in patients with type 2 diabetes. Since insulin and amylin work as partner hormones to decrease postprandial glucose levels, replacing amylin can fulfill some of the unmet clinical needs of insulin-using patients,

such as persistent postprandial hyperglycemia, and wide fluctuations in glucose levels implicated in the development of diabetic complications, hypoglycemia, and weight gain. Thus, the addition of pramlintide to insulin therapy constitutes a more physiological approach to postprandial glycemic control compared with using insulin alone.

In January 2006, a group brought together by Dr. Irl Hirsch met in Washington, D.C., to develop practical guidelines for using pramlintide with insulin – the group was a virtual who's who of diabetes therapy and treatments, and included Drs. Larry Blonde, John Buse, Steve Edelman, Satish Garg, Jay Skyler, and Carol Wysham, in addition to star educator Virginia Valentine. The main safety concerns associated with pramlintide are insulin-induced hypoglycemia and nausea during initiation of therapy. These side effects can be attenuated or prevented by individualizing insulin dosing and timing regimens in relation to mealtime, frequent SMBG, and gradual titration of pramlintide. Thus, the panel's major recommendation was that optimal approaches to initiating pramlintide vary according to patient. More detailed consensus recommendations included:

Proper patient selection – The panel specified that insulin therapy must be optimized to reach A1C goals as a prerequisite for starting pramlintide. They encouraged the use of insulin analogues in an individualized basal-prandial insulin program via multiple daily injections or an insulin pump before starting pramlintide. Ideally, a detailed log of SMBG readings (preferably six tests per day, but no fewer than one before each meal and at bedtime), medication, food, and exercise should be maintained over the week prior to starting therapy so that treatment can be individualized to the greatest extent possible.

Contraindications – Contraindications to pramlintide include hypoglycemia unawareness, eating disorders, severe gastroparesis, or the use of drugs that stimulate GI motility. Due to the difficulty of diagnosing gastroparesis, the panel specified that only patients with severe gastroparesis requiring hospitalization should be deemed ineligible for pramlintide therapy. In fact, pramlintide may help in cases of mild gastroparesis made worse by overeating. Although the package insert says that pramlintide is not recommended for patients with A1C > 9 percent, the panel preferred more flexible parameters to accommodate individual circumstances.

Pramlintide dosing – For type 1 patients, the panel endorsed a 15 µg (2.5 unit) starting dose, reducing the dosage to as low as 6 µg (1 unit) in the event of significant nausea, followed by slow upward titration (as gradual as 1 unit at a time). They also felt that gradual titration to a dose exceeding the manufacturer's maximum recommended dose of 60 µg (10 units) might be warranted in certain patients to achieve optimal results. For type 2 patients, they recommended a starting dose of 60 µg (10 units) injected immediately before main meals, and increased to 120 µg (20 units) as tolerated. In all cases, they recommended frequent SMBG to match pramlintide doses with insulin, especially during the adjustment phase.

Pramlintide timing – The package insert recommends administering pramlintide just before the meal, based on a dose-timing study. However, empirical evidence indicates that injecting pramlintide earlier (i.e., up to 15 minutes before mealtime) increases satiety in some patients, while administering pramlintide as close to the meal as possible reduces nausea in others.

Dosing of prandial insulin and oral antihyperglycemic agents – Although the prescribing information recommends reducing preprandial insulin doses by 50 percent, the panel suggests a range of 25 percent to 50 percent for type 1 patients. Since pramlintide slows the appearance of glucose in the circulation, the panel also strongly advocated administering rapid-acting insulin near the end of the meal or immediately after the meal, when the dose can be calculated based on the food consumed and the release profile may be better matched with glucose entry into the bloodstream. Patients can resume pre-meal injections once the effect of pramlintide on satiety becomes known.

For type 2 patients, the panel suggests a zero to 25 percent reduction for patients when A1C is > 8.0% and a 25 to 50 percent reduction when A1C is < 8.0%. The panel also advised reconsidering the use of oral antihyperglycemics when starting pramlintide to reduce the risk of hypoglycemia.

Although the manufacturer recommends separate injections of insulin and pramlintide, the panel was divided on whether mixing pramlintide with insulin was a reasonable option for type 2 patients concerned about additional injections. They therefore recommended further study of this off-label use.

Preventing hypoglycemia – Although pramlintide itself does not cause hypoglycemia, the addition of pramlintide to insulin therapy may increase the risk of insulin-induced hypoglycemia. Thus, the manufacturer recommends that patients taking pramlintide check blood glucose pre- and post-meals, before driving, and at bedtime. The panel also recommends prescribing injectible glucagon and keeping oral glucose on hand to ensure rapid treatment of hypoglycemia.

Managing nausea – The panel emphasizes not to rush dose titration. Anecdotal reports indicate that administering pramlintide as close to the meal as possible might also minimize nausea. Nausea often dissipated with time.

Follow-up – Patients beginning pramlintide should be contacted within the first week to review their SMBG data and scheduled for an office visit within 4 weeks.

Policy change and future research – The panel also recommended additional research, reimbursement reform, and development of alternative delivery routes and extended-release formulations of pramlintide.

The complete article is available at http://www.closeconcerns.com/press/Consensus_Development_Conference.pdf under the press link on the homepage.

—by Rachael Hartman

6. Diabetes in the Media: *Arthur* features a pediatric pump patient – clear LifeScan win!

Arthur has discovered diabetes. And why not? As diabetes has found its way into many corners of American pop culture, it was only a matter of time before it was featured in a cartoon. In this case, diabetes was part of the beloved PBS cartoon *Arthur*, based on the popular books by Marc Brown. The episode in question features an actual girl, named Corinne, who discusses her condition, displays her Animas insulin pump, and even demonstrates LifeScan UltraSmart blood glucose monitoring – J&J couldn't have hoped for better product placement… The episode first aired on May 17 but was rebroadcast many times over the summer.

In the cartoon portion of the show, called "Desert Island Dish," the teacher, Mr. Ratburn, gives Arthur and the class an assignment: if you could choose an unlimited supply of one kind of food to take to a desert island, what would it be? The students return with their answers: BBQ potato chips, Kotton Kandy Krunch, Ice Cream, etc. Mr. Ratburn finds nutritional faults in each one. So the students consult a food pyramid, but unable to find the perfect food, they decide to complete the assignment as a group project, where everyone picks a different food group. Mr. Ratburn is pleased.

After the segment, Corinne introduces herself and her friends, who are making healthy snacks. The cute 12-year-old with dark hair and freckles says she has diabetes and explains what that means, using her devices to help. At one point, she holds up her clearly labeled OneTouch UltraSmart and says: "You take

something called a meter, you put a little strip into it; and then you prick yourself with the little needle, and you put the blood onto the strip and it reads how much sugar is in that sample of blood."

We're not sure how the directors chose Animas and Johnson & Johnson, but they certainly did their bit for making diabetes a little hip - we're all for that. You can purchase the episode "Desert Island Dish" on Google Video (video.google.com) for $1.99.

—by Dan Belkin

7. DCU Lit Review: DPP-4s associated with cancer? Not so fast…

Below is our list of the top 25 articles on diabetes that have been published since our last DCU. Our team is always looking for the most relevant articles on new diabetes research, and this month we've compiled a list that includes papers from journals such as *Diabetes Care, Diabetologia, NEJM, Lancet, Pediatric Diabetes*, *Science,* and more. This month we feature an original research article on potential DPP-4 inhibitor toxicity published by Masur and colleagues in *Regulatory Peptides*. With the anticipated FDA decision date drawing near for Merck's DPP-4 inhibitor Januvia, we were fascinated to see this paper on some possible side effects with this class of drugs. Masur and colleagues performed their experiments at pharmacological concentrations of DPP-4 inhibitors - much higher than the concentrations that patients would experience in their blood plasma - so the clinical relevance of their work is certainly questionable. Still, we think it's perfectly possible that DPP-4 inhibitors will run into toxicity issues in a small subset of patients once they become widely prescribed, considering how many natural substrates of DPP-4 exist in the body. It's not surprising that research groups would be looking for problems with this class; they really aren't that potent, so any major toxicity issues could be strong evidence against using them. That said, it's hard to prove toxicity from Petri dishes, especially given the timing that would be required, so we don't look for this to be a major strike against the class – at least, not at this point. Our full review follows, along with our list of top picks from the journals.

Masur K, Schwarz F, Entschladen F, Neggemann B, Zaenker KS. "DPPIV inhibitors extend GLP-2 mediated tumour promoting effects on intestinal cancer cells." *Regulatory Peptides* (2006), Article in Press.

In this paper Masur and colleagues look at the effects of DPP-4 inhibitors on the growth and migration of human colon cancer cells in vitro. The two cell lines they used were SW480 (grade IV, poorly differentiated) and HT29 (grade I, well differentiated) human colon carcinoma cell lines. They verified that both cell lines express the GLP-2 receptor through imunnohistology with GLP-2R11A, a polyclonal anti-GLP-2 receptor antibody from Alpha diagnostics.

Exposure to GLP-2 increased the rate of spontaneous migration in SW480 colon cancer cells. SW480 cells have a high spontaneous-migration rate of 19.8 ± 2.4 percent and are commonly used to study tumor metastasis. This rate of migration increased to 27.6 ± 3.8 percent when the cells were treated with 1 nM GLP-2, to 32.5 ± 4.0 percent when they were treated with 10 nM GLP-2, and to 44.6 ± 4.2 percent when they were treated with 100 nM GLP-2.

The effect of GLP-2 to increase migration of HT29 cells was assisted by DPP-4 inhibitors. As in SW480 cells, treatment of HT29 cells with GLP-2 increased the rate of migration in a dose-dependant manner. However, the increased migration rate only persisted for six hours due to what the authors believe is degradation of GLP-2 by endogenous DPP-4. When they added the DPP-4 inhibitors Diprotin A (Sigma, Deisenhofen, Germany) or P32/98 (Biomol GmbH, Hamburg, Germany) to the cells along with GLP-2, they did not observe this time-dependent loss of increased migratory activity; and the rate of activity was also increased. Treatment of HT29 cells with 10 nM GLP-2 alone increased migratory activity by 18.7 ± 3.9 percent, but treatment with 100 nM P32/98 and 10 mM GLP-2 increased migratory activity by 26.9 ± 4.4 percent.

GLP-2 treatment but not DPP-4 inhibitor treatment increases SW480 cell proliferation by decreasing doubling time. Treatment with 10 nM GLP-2 decreased doubling time from 2.4 days to 1.5 days. Addition of 100 nM P32/98 to 10 nM GLP-2 did not increase this effect.

There is no indication that DPP-4 inhibitors could cause cancer. The authors suggest that these findings indicate the inhibitors may increase the probability of tumor metastasis in patients with pre-existing colon cancer. However, the clinical relevance is far from clear. Notably, not only was the study performed *in vitro* rather than *in vivo*, the authors used extremely unphysiologic concentrations of GLP-2 to perform their experiments. Normal human plasma concentrations of GLP-2 are in the picomolar range (~3 pM GLP-2). The experiments performed in this study used GLP-2 in the nanomolar range (from 1-100 nM GLP-2), three orders of magnitude or higher than would occur in healthy humans. Based on the logarithmic relationship between GLP-2 concentration and migratory activity that the authors observed in their experiments, the picomolar concentrations of GLP-2 that exist *in vivo* should cause no significant increases in migratory activity. This is why we don't see any clinical relevance in these findings – GLP-2 concentrations are simply not this high in humans. The GLP-2 concentrations that the authors used were so high that the tumor-promoting effects they observed may have come from nonspecific binding to growth hormone receptors on the tumor cells and not specific binding to the GLP-2 receptor at all. This is a possibility for any peptide at unnaturally high concentrations, not just GLP-2.

As a reminder, DPP-4 inhibitors do not themselves promote either tumor proliferation or migration; the authors simply showed that unnaturally high concentrations of GLP-2 might. Notably, the two DPP-4 inhibitors that the authors used are not currently under clinical development. Diprotin A and P32/98 are both DPP-4 inhibitors out of biochemistry supply catalogs, and though the authors observed similar results with both, those results cannot simply be generalized to sitagliptin and vildagliptin.

However, we would like to see some data on the plasma concentrations of GLP-2 in patients on long-term DPP-4 inhibitor treatment. As we noted above, normal plasma levels of GLP-2 are in the picomolar range, too low to promote tumor proliferation and migration. But it is theoretically possible that long-term treatment with DPP-4 inhibitors causes accumulation of GLP-2 in the body over time. If patients treated with sitagliptin or vildagliptin for an extended period of time achieve high levels of GLP-2 similar to those used in this study, they may be prone to higher rates of metastasis. This possibility, though remote, is worth checking.

Though the results published here appear negative for Merck and Novartis, we don't foresee actual significant negatives on sitagliptin and vildagliptin. However, this study does remind again of the need for long-term safety studies before we can be sure that DPP-4 inhibitors don't cause side effects in subsets of the population.

Recent top clinical lit picks…

August 2006

- *Arch Intern Med* - Blood glucose & mortality in hospitalized nondiabetic patients with heart failure - Barsheshet
- *Diabetes Care* - AACE and ADA consensus statement on inpatient diabetes and glycemic control
- *Diabetes Care* - Clinical observations of exenatide treatment - King
- *Diabetes Care* - Adherence to insulin and the risk of glucose deterioration - Blaha
- *Diabetes Care* - Longitudinal study of new and prevalent use of SMBG - Karter
- *Diabetes Care* - A critical appraisal of the continuous glucose-error grid analysis - Wentholt

- *Diabetes Care* - Prevalence of cardiovascular-disease risk factors in U.S. children and adolescents with diabetes: The SEARCH for Diabetes in Youth Study - Rodriguez
- *Diabetologia* - Vildagliptin reduces postprandial intestinal triglyceride-rich lipoprotein particles - Matikainen
- *Lancet* - Editorial - Should we continue to use BMI as a cardiovascular risk factor? - Franzosi
- *Lancet* - Association of bodyweight with total mortality & cardiovascular events in coronary artery disease - Romero-Corral
- *NEJM* - Overweight, obesity, and mortality in persons 50 to 71 years old - Adams
- *NEJM* - Body-mass index and mortality in Koreans - Jee
- *NEJM* - Editorial - ATP-sensitive potassium channels - Sperling
- *Nat Clin Pract Endo Metab* - Childhood obesity: behavioral aberration or biochemical drive? - Lustig
- *Pediatric Diabetes* - Predictors of fear of hypoglycemia in adolescents with type 1 diabetes - Gonder-Frederick
- *Regulatory Peptides* - DPP-4 inhibitors extend GLP-2-mediated promoting effects on intestinal cancer - Masur
- *Science* - Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes - Ozcan

September 2006

- *Clin Chem* - Editorial - Do we know how to diagnose gestational diabetes mellitus? - Pettitt, Jovanovic
- *Clin Chem* - Lack of concordance between the 75-g and 100-g glucose load tests for diagnosis of GDM – Mello
- *Diabetes Care* - OmniPod System: Patient perceptions, preference, and glycemic control - Zisser
- *Diabetes Care* - Exposure to rosiglitazone and fluoxetine in the first trimester of pregnancy - Choi
- *Diabetes Care* - Third Annual World Congress on the Insulin Resistance Syndrome - Bloomgarden
- *Diabetes Care* - National study of U.S. emergency room visits with diabetic ketoacidosis, 1993-2003 - Ginde
- *Diabetes Care* - Nutrition recommendations and interventions for Diabetes-2006: A position statement of ADA
- *Diabetes Care* - Lower baseline glycemia reduces oral agent glucose-lowering efficacy - Bloomgarden

—by Jenny Jin and Kelly Close

8. Local radio interviews Dr. Robert Lustig on a new theory about childhood obesity

Dr. Robert Lustig, UCSF pediatric endocrinologist, has drawn considerable attention for his provocative ideas on how modern diets are leading to childhood obesity. His recent appearance on Michael Krasny's Forum, a live local radio program in the Bay Area, reminded us of the intense interest that surrounds his work.

In the interview, he discussed his hypothesis that diet-induced leptin and insulin imbalances are the cause of our current childhood obesity epidemic. This hypothesis is also described in greater detail in his recently published review article in *Nature Clinical Practice Endocrinology & Metabolism* (August 2006; 2(8):447-458). Dr. Lustig's theory begins with the basic idea that childhood obesity reflects the poor quality of our modern diets, but the problem is not a simple matter of eating too much and exercising too little. Rates of pediatric obesity have actually risen fastest among 2-to-5 year olds, when children have very little control over what they eat. Obesity among these children cannot be a matter of personal irresponsibility, which leads Dr. Lustig to conclude that some physiological imbalance is occurring.

Like most nutritionists, he believes that modern diets replete with processed foods contain too much sugar and too little fiber, both factors that tend to increase insulin production. We know obesity and hyperinsulinemia usually go hand in hand, but Dr. Lustig's hypothesis turns the causality of the two

backwards by suggesting that hyperinsulinemia may actually cause obesity, not the other way around. He believes that insulin has very different acute and chronic effects. Acute administration of insulin curbs appetite, but chronic hyperinsulinemia may actually cause hunger by resetting the leptin pathway.

Leptin mediates appetite and metabolism. Normally when people diet their leptin levels fall and in response their body goes into what Dr. Lustig calls "starvation mode," when the metabolism slows down and a certain portion of all calories consumed are routed automatically to fat without ever being made available to the muscles to burn. Obese individuals tend to have leptin resistance, which is a condition in which the body remains in starvation mode even when there are high circulating levels of leptin. It makes sense from an evolutionary standpoint that hyperinsulinemia might cause leptin resistance; linking the two metabolic pathways in this manner would have been a useful adaptation during pregnancy and puberty, when individuals need high insulin and weight gain in order to support fast growth. Unfortunately, for people who are not pregnant or in puberty, this phenomenon tends to lead to obesity.

The most interesting consequence of this theory is the way it reverses the etiology of obesity. Instead of assuming that gluttony causes obesity, this theory posits that poor diets (high in sugar, low in fiber) cause hyperinsulimenia, making perfectly normal people go into 'starvation mode.' Once this happens, things just start rolling downhill: everything they eat automatically contributes to weight gain, which means that those calories which are being routed to fat are not available for energy, so they feel hungry and eat even more. Obese people may actually overeat because their bodies think they are starving.

Though the following wasn't mentioned on the radio program, from a clinical treatment standpoint we note that Dr. Lustig has done studies with obese children who have hyperinsulimenia because of a dysfunction of the vagus nerve which mediates beta cell hyperactivity and insulin over-secretion. This syndrome is treatable by insulin suppression and may exist in up to 20 percent of all obese individuals.

Of course, program host Michael Krasny and call-in listeners were all curious about what can be done to reverse this vicious cycle. Dr. Lustig's answer: we should return to the kind of diet we consumed in the 1950's and earlier, before processed food began to dominate the diet landscape. For example, rather than consuming a 120 kcal serving of orange juice we could consume a 20 kcal orange, which not only has fewer calories but also contains a great deal of fiber. Dr. Lustig lamented the fact that the average daily consumption of fiber today is only 10 grams, compared to the 100-300 grams of daily fiber that people consumed before the advent of processed foods.

Dr. Lustig was relatively cynical about the role of food companies, drawing comparisons between big food and big tobacco. He noted that Altrea, which owns Kraft and Nabisco, also owns Phillip Morris. This is why, he believes, it's necessary for the government to begin regulating the distribution of processed foods to children, just as they did with tobacco. He shared a poignant anecdote about a 6–year-old patient who weighed 100 lb; the boy was wider than he was tall. Surprisingly, when Dr. Lustig took the boy's history from his mother (in Spanish, the family was Hispanic), he found that the child didn't drink soda at all. However, he did drink a gallon of orange juice a day. When Dr. Lustig explained to the boy's mother that oranges are good but orange juice is bad, she paused and asked, "Then why does WIC give it to us?"

WIC (Women, Infants, and Children) is a federal USDA-funded food and nutrition service program for, among others, children up to age five who are at nutritional risk. Unfortunately, in this case, by providing the processed version of a healthy fruit, the program did exactly the opposite of its intention. Dr. Lustig noted that while California's WIC program now provides fresh fruit, this is not yet the case in all states, which means the lowest-income children who are at highest risk of obesity have to consume the processed version… all of which leads back to the problem of diet-induced hormonal imbalance.

—by Jenny Jin

9. Upcoming Conference Preview

- **EASD, September 14-17, Copenhagen, Denmark http://www.easd.org/** – We're excited to attend the 42nd annual EASD meeting in Copenhagen/Malmoe. As you know, the big ticket item at this year's meeting will the DREAM trial results, which will be presented in an oral session on Friday, September 15, from 5-7:30 p.m. in August Krogh Hall. As we prepare for the meeting, we thought we'd share some of the other oral sessions and posters that we're looking forward to.

  Thursday, September 14, 2006
  The opening lecture will be given by Dr. Edwin Gale, a UK researcher, on "Discovering Diabetes." The most intriguing oral presentation (OP) for the breakout session that follows is OP 1: "Novel treatments for diabetes," which will feature talks on abstracts about exenatide, exenatide LAR, liraglutide, and sitagliptin. Later in the day we'll also visit OP 7: "Novel therapies - type 2 diabetes," which looks in more detail at studies of the two big DPP-4 inhibitors, sitagliptin and vildagliptin. At the end of the day are two symposia of note: the EASD/ADA symposium on metabolic risk in diabetes and the EASD/JDRF symposium on new developments in the pathogenesis and therapy of type 1 diabetes. Together the two will address some of key questions in both subtypes of diabetes.

  Of course, the vast majority of EASD abstracts will be presented in poster sessions, not oral presentations, and there are so many of interest that it's hard to pick just a few. Three poster sessions (PS) on new drugs and technologies of particular note occur during Poster Event A on Thursday - these are PS 61 on DPP-4 inhibitors, PS 79 on continuous glucose monitoring and PS 85 on inhaled insulin. Poster Event B, which follows directly after Poster Event A, also features several sessions worth looking into, including PS 62 on oral agents (new drugs and new combinations) and PS 68 on preclinical novel therapies.

  Friday, September 15, 2006
  Friday morning will begin with a host of what promise to be interesting talks. Two to highlight are the EAS/ESC/EASD symposium, entitled "Strategies to fight cardiovascular disease in diabetes; from basic science to clinical practice," and the lecture on AGEs and diabetic complications. Several of the late morning oral presentations will also look at progression, metabolism, and CVD – key themes, needless to say, in type 2 care. Also included on our list is OP 18: "Diabetes in pregnancy," which brings together abstracts from the rather scarce pool of pregnancy studies. In the afternoon are two other oral presentations worth noting, OP 19: "Lessons from clinical studies," and OP 20: "Glucose metabolism and the brain," which we mention because of all the media attention lately on links between diabetes and Alzheimer's disease, dementia, and strokes. And, of course, the biggest oral presentation of all will be the late afternoon presentation of the results of the DREAM trial.

  Poster Event C on Friday includes several sessions on type 1 diabetes, such as PS 3: "Genetics of type 1 diabetes" and PS 21: "Immunopathogenesis of type 1 diabetes." Also worth looking at are sessions on the psychological implications of diabetes, childhood effects of the disease, and neuropathy complications. Poster Event D also features sessions on complications, as well as a host of sessions on obesity.

  Saturday, September 16, 2006
  Again, many interesting talks to choose from in the morning; the evidence-based medicine debate (subtitled "metformin as first choice in oral diabetes treatment: walking on solid ground or skating on thin ice") draws us in, but we're also extremely interested in what Drs. Phillip, Buckingham, and Tamborlane have to say in their talk on closing the loop with CSII and continuous glucose sensing. We'll be covering both, no worries …Two oral presentations we'd like to single out from the late-morning breakout sessions are OP 25 on insulin therapy and and OP 30 on diabetes in childhood. The

former will include a few abstracts on the new insulin detemir and the latter, of course, addresses the growing problem with childhood obesity. Inhaled insulin will be addressed in OP 31 and other compounds of interest including Novo's liraglutide and Amylin's leptin will be discussed in OP 36: "New therapies - pre-clinical." The day will finish with the 41st Minkowski Lecture to be given by Dr. Michael Roden, who will speak on overabundance.

As always, we're interested in incretin hormone studies, which Poster Event E will certainly offer in PS 47: "Metabolic effects of incretin hormones." It looks at GLP-1, GIP, and DPP-4 inhibitors. Also of interest are PS 83: "Insulin trials in type 2 diabetes" and PS 89: "Hypertension" – both insulin and antihypertensives are underused in type 2 patients so any interest in either is good news. Poster Event F offers another session on incretins, PS 60: "GLP-I analogues and incretin effect" as well as a session on hypoglycemia, which has several abstracts on CGMS that we can't wait to see.

Sunday, September 17, 2006
Some very good presentations are promised for the final day! OP 38: "Postprandial glucose regulation" shows data on this area of glycemic variability that always interests us so much, while OP 43: "Continuous glucose monitoring" looks at several CGM studies – we are always eager to see new data on this front. To close the conference, Dr. Leif Groop will give the 38th Claude Bernard Lecture on the genetic complexity of type 2 diabetes.

- **Cardiometabolic Health Congress, Oct 19-21, Boston, MA** **http://www.cardiometabolichealth.org** – Dr. Jay Skylar, Dr. Christie Ballantyne, and Dr. Richard Nesto will be chairing this conference on the management of cardiometabolic risk and metabolic syndrome, featuring talks from many prominent physicians. A little background: as many readers know, last September ADA and EASD published a statement in *Diabetes Care* questioning the usefulness of 'metabolic syndrome' as a diagnostic condition, citing issues with the syndrome's ambiguity. When the statement generally seemed a disagreement between ADA and AHA, the two organizations published a joint statement in *Diabetes Care* this July promoting the term 'cardiometabolic risk' as a better way of describing the increased risk of diabetes and cardiovascular disease in people with pre-diabetes, hypertension, dyslipidemia, and obesity. So far this joint statement has not actually resolved the ADA/AHA debate; AHA continues to use metabolic syndrome as ADA promotes the idea of cardiometabolic risk. We're curious about whether this conference represents a new level of consensus between the two organizations. Notably, AHA President Dr. Robert Eckel, who has historically advocated the use of metabolic syndrome, will be speaking at several sessions… all of which use the term 'cardiometabolic risk.' We believe, a year from now, it'll be well part of commonly used diabetes terminolaogy. Another session of note will be the keynote presentation by Dr. Jean-Pierre Després on "Assessing Global CVD and Type 2 Diabetes Risk: From Metabolic Syndrome to Cardiometabolic Risk." A complete program is now available at the conference website – we're looking forward to this conference *incredibly* as we need to do much more learning in this arena, which promises to grow and grow in importance.
- **NAASO, Oct 20-24, Boston, MA** **http://www.naaso.org** **–** Sessions at this year's annual scientific meeting span fields from anthropology to molecular biology and apply to aspects of treatment from clinical management to counseling. Themes include Cell and Molecular Biology, Integrative Biology, Clinical Studies, and Population Studies. With five full days of lectures and workshops, not to mention the presentation of over 900 abstracts, it is clear there is lots of potential learning here at hand – especially if you combine going with the Cardiometabolic Health conference noted above. And Boston in the fall – what's not to like!
- **DTT, Nov 2-4, Atlanta, GA** **http://www.diabetestechnology.org/** – The sixth annual meeting of the Diabetes Technology Society features an extensive survey of new technology for both the patient and clinician. Major topics include technology for metabolic monitoring, formulas for expressing continuous blood glucose data, the artificial pancreas, and delivery technologies for insulin and other

peptides. In addition, the meeting promises a discussion of educational technology for patient empowerment, the creation and application of patient databases, and reimbursement strategies including coverage of devices and drugs and perspectives of managed care.

- **Insulin Congress, Nov 10-12, Washington, DC** http://www.insulincongress.org – The first meeting of the Insulin Congress! The planning looks quite something for this and there are many sessions that look quite compelling – this is definitely a conference that will go a level deeper. For example, we'll learn more about insulin and endothelial function, about using symlin to reach targets (and we're likely not talking just about A1Cs), optimizing use of Byetta, and treatment of inpatients by non-specialists,

—by Alyssa Shell, Jenny Jin, and Kelly Close