

DIABETES CLOSE UP

Diabetes Close Up
January 2007, No. 65
Earnings up close ...

The Shorter Version

From the Editor:

It's suddenly February, and while much of America will be watching the Super Bowl this Sunday, we'll be in Montpellier, France, for the European Diabetes Technology meeting. While we'll miss the football parties, we'll still get to drink a glass of Bordeaux and nibble on some excellent sausage and cheese. More important, we'll get to take a closer look at the technological strides overseas and to catch what might be in abstract form at ADA. We'll then rush back in time for the ADA Postgrad in New York in late February, at which point we'll report back to you.

On the topic of ADA Postgrad, Close Concerns is co-sponsoring a breakfast with diabetes luminaries Drs. Irl Hirsch and Jay Skyler with biotechnology analyst and diabetes expert Mike King of Rodman and Renshaw. We are most eager to hear the good doctors expound on incretins, DPP-4 inhibitors, inhaled insulin, prospects for new drugs like Galvus, LAR, etc., and to hear Mike prod them about all their current clinical practices (and to help him to this). If you'd like to come to breakfast, please e-mail me – I think most spots are taken, but Mike is such a nice guy, maybe we can talk him into expanding the audience ever so slightly. This isn't one to miss ...

Nor is this issue one to miss! Speaking of Dr. Hirsch, we have an eight-page interview with him this issue, where we prime him for his latest thoughts on continuous glucose monitoring and glycemic variability, incretins, and the dismal state of diabetes care in America. Dr. Hirsch discusses the crisis in endocrinology – we have a severe shortage of endos, and the problem is getting worse. This topic is of particular interest to us, perhaps because several at DCU rely on endocrinologists for our care. In the coming months, we'll be discussing our survey of medical school students, which asked what specialties appealed to them. Here's a hint that likely won't surprise you: Diabetes isn't one of them.

On a more positive note, we have an important story on how pharmacists can fill the clinical breach for diabetic patients; a program in Asheville has had considerable success and is now spreading to other cities across the country – we expand on the recent, excellent, NYT piece you may have seen. We also have an outstanding conference report from the Keystone Symposia on Diabetes and Obesity, in which attendees – ignoring the temptations of glorious, snow-covered mountains – heard important presentations on the brain and how it controls metabolism. Very interesting, hard-core basic science stuff – Dr. Daniel Drucker spoke there and although the conference was a bit removed from his usual translational focus on how to treat diabetes, we were very interested to hear him, particularly his statements on beta cell regeneration. Such conferences always have their playtime, but we're pretty good about sticking to the business at hand. That's because we love this field and care about the people who are in it, even if it means missing the fun and games back home.

—Kelly L. Close

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Quotable Quotes from January’s DCU:

Dr. Irl Hirsch, University of Washington

- **On CGM:** “We need to all remember they are first generation and they will all improve. Obviously, they are not yet perfect, but for people who understand how to use trends in addition to SMBG, our initial experience has been great.”

- **On inhaled insulin:** *“Inhaled insulin may be great for some patients, but it obviously doesn't appear the market is ready. My take is that the insulin will need to be easier to administer than the Exubera is, and the insulin will require some type of pharmacokinetic/pharmacodynamic advantage. That is why I think both the Lilly preparation and Mannkind insulin will do better.”*
- **On incretin therapies:** *“Insulin is still the cornerstone of all of diabetes therapy. It may be that like with the introduction of troglitazone 10 years ago, the greatest impact on insulin growth will be the DPP-4s since they are oral and much easier for the primary care physicians to prescribe. The field is becoming so crowded so fast, that many are finding it difficult to keep up with all of these new choices. The added choices are a good thing, but to keep A1C levels within target (which as a group we have not done very well with) insulin will still be required. To me, the real question is what happens after many years of some of these newer therapies (like Byetta) that may have B-cell preservation qualities?”*
- **On Byetta in pre-diabetes:** *“My guess is Byetta would be a tremendous agent for pre-diabetes. The key would be if the beta cell benefits are true in humans like we think they are, this could be a big hit. The weight loss and the reduction of postprandial glucose levels may make this a homerun for this population. BUT, if the B-cell benefit is real, what about Byetta (or even a DPP-IV) for preclinical type 1 diabetes?”*
- **On Insulet's OmniPod and the prospect for pump therapy:** *“I like it a lot... OmniPod is a fabulous pump ... I think the market would be bigger if the pump companies would do a better job of training doctors, especially training fellows. You know the endocrine fellows in training have been sort of ignored for years. All the insulin companies and I think all of the pump companies are realizing that they have to acknowledge them and acknowledge their presence because these are the guys who would be going into practice prescribing pumps and insulin and expensive oral agents. When you hit them really for the first time once they're in practice it's kind of late,,,:*

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.

- **January 30: Prevention is better than cure**
- **January 19: Can a businessman save the Joslin Center?**
- **January 16: Insulin shock: Eli Lilly loses loyalty of one-time faithful customers**
- **January 13: Like TZDs but no weight gain? InteKrin's new drug has intriguing prospects**
- **January 11: Walking yourself into a long life**
- **January 11: Surprising slowdown in healthcare cost growth**
- **January 11: Ideal BMI ratio? It's in the eye of the beholder**
- **January 10: Novo hires star Dr. Nathaniel Clark**
- **January 7: Under-reported, under-recognized, and under-appreciated: A New York Times essay misdiagnoses an epidemic**
- **January 6: More payouts from Lilly and more questions (16% patients in clinical trial gained over 66 pounds each ...)**
- **January 4: Eli Lilly under more fire with Zyprexa**
- **January 4: Workplace Blues: A Peer Speaks Out Against Her Own**
- **January 3: Better Fit or Fat? The New Republic's argument for obesity**
- **December 30: Three cheers for pharmacists ~ and the visionaries behind the Asheville Project**
- **December 29: Sontra closes down, still amidst revolutionary claims...**
- **December 28: The Trendiest Cardiometabolic Risk Factor**
- **December 27: Second in a series: grim thoughts on dialysis**
- **December 26: More on diabetes and disabilities**
- **December 26: Medical Care – pay for performance**
- **December 25: NYT, Sonny Kleinfeld on Diabetes and Laws**
- **December 23: UN resolution on diabetes passed!**

The Longer Version

1. DCU Company Watch

- **Lilly 4Q06—Tough diabetes market on market share front— thankful for Byetta:** Overall Diabetes Care revenues increased 4% in Q4 to \$781.7 mm compared to a year ago. (This compares to 9% growth at Q3). US revenues increased 4% to \$451.2 mm; rest-of-world revenues were up 5% to \$330.6 mm. For FY06, revenue increased 6% up to \$2.959 b – so disappointing to come so close but miss \$3 billion! Excluding the very large decrease in Actos revenue due to a step-down agreement with Takeda on Actos royalties, Diabetes Care revenue would have increased 17% in Q4 and 10% for FY06. Lilly's insulin performance continues to suffer although management says the share bleed has stabilized. We assume they will however continue to lose share to the market shift to long acting analogs even if competitively they do better with rapid acting Humalog. Lilly announced Jan 11 that it would stop construction on a \$425 mm insulin manufacturing plant in Prince William County, Virginia, because global demand for insulin “isn't meeting the levels projected” when Lilly planned the plant in 2003. Overall diabetes revenues increased 9.6% for the year (compared to Novo's 15%). Lilly is hopeful about re-energizing its sales force, noting a recent restructuring and the launch of 3 new pens, including a “smart” pen. Lilly is increasing its use of contract reps by 40%. We see how contract reps offer financial flexibility but confess to some skepticism about the ultimate alliance of rented help in the field relative to committed reps – although there are certainly many CDEs in the US whose help they would be lucky to have. One of the pens, the Memoir, looks very interesting in that it can remember the last 16 doses of insulin but we don't see that market making the major difference in sales in 2007. Notably absent was any conversation about LAR and Lilly's previously mentioned internal GLP-1 program. At this point, on regulatory timing, LAR looks to be a bit behind Novo's liraglutide, which has finished phase 3 enrollment and with plans for submission in mid-2008. LAR certainly represents the breakthrough product of the two in our view though if there are Byetta and liraglutide out without LAR, Novo will use formulary strength and discussion of lower fasting rates to market liraglutide. On Arxxant, management said that active appeal discussions with the FDA are ongoing and that they will have more to say on the subject in 1H07 – it would be a major win if Lilly is successful in turning around the FDA's approvable letter and convincing the agency not to require another long-term trial.
- **Novo 4Q06—Continuing gains insulin market share worldwide – mostly at LLY's expense:** Management reported Jan 31 that overall growth in Novo's diabetes franchise was an impressive 15% with North American share of the insulin market up to 41%, ahead of Sanofi's mid 20% and Lilly's deteriorating sub 30%. Diabetes sales in 4Q06 were \$1.31 b, up 9.6%, and were \$4.82 b for the full year, up 15%. Diabetes contributed 77% of Novo's overall sales growth for the year. Management set growth expectations (which are primarily driven by insulin) at about 10%, citing possible competition from Exubera and to a lesser extent, Byetta and Januvia. Novo said that Byetta has caused some insulin use to decrease but it isn't expected to be an issue because the overall market continues to grow; Novo is more concerned about Exubera and will watch Pfizer's DTC efforts closely. We thought the remarks were candid and welcome – with 500,000 people on Byetta in the US, we could definitely see how some movement to insulin is delayed though we also wonder about the impact on the awareness about staying in control and keeping A1c in control or reaching control – we would think that would be a positive message, especially with 1 – 1.5 million additional type 2 diagnosed patients in the US alone each year. We would be very surprised if Exubera emerges as a real threat near-term, given product complexity issues, reimbursement hassles, and long-term safety questions. Liraglutide phase 3 has completed enrollment – data expected in 2H07; mid-2008 regulatory filing expected. We note that this timeline is ahead of Amylin/Lilly's LAR program, which is expected to complete enrollment in Q1 with submission in late 2008, by at least a quarter, possibly two. As a reminder, we learned January 15 that Novo is discontinuing development of all oral drugs. Novo

initiated a 20-week, 550 patient dose ranging study looking at liraglutide for obesity. Treating obesity seems a logical companion to treating diabetes. While there aren't company-sponsored obesity studies for Byetta that we know of, we imagine those resources might be saved for LAR. Little mention of AERx in the presentation, beyond a remark that Novo has not yet secured a manufacturing facility for the product. An increase of Novo's US sales team from 1,200 to 1,900 reps will be finished 1H07.

- **Amylin 4Q06—Good report, fascinating PsychoGenics deal:** Amylin reported Jan 30 and the main takeaways were that Byetta continues to grow despite noise from Januvia's launch, that Symlin is a sleeper drug with great promise, and that the preclinical and early-stage pipeline continue to be undervalued. As we heard at the always-stellar JPMorgan conference earlier this month, the LAR manufacturing plant is still on track for a late 2008 completion. Amylin expects to complete phase 3 enrollment in Q107 with data available in the second half of the year – we can't remember a trial that had enrolled patients or PIs more excited. As we also learned at the JPM conference, Amylin has completed engineering runs at the commercial scale – mitigating some manufacturing risk, in our opinion. We look for Symlin pen approval and label expansion for use with basal insulin in the second half of the year – we expect that to give sales a pop. Last, Amylin has a new partnership for neurohormones for psychiatric disorders – this is very interesting given that we have personally seen so much success with Symlin. We certainly wouldn't be surprised to see new psychiatric indications. A release on the PsychoGenics website notes that a new company, Psylin Neurosciences, has been formed and will focus on these new indications – now that's one company we'd love to invest in. The other big-but-expected news today is that the very-together Dan Bradbury will be taking over as CEO on March 1 from the very-together Ginger Graham – thank God she will still be on Amylin's board of directors. And hey, consider what those meetings must be like? Along with Graham, other members of Amylin's BOD include the awesome (in the true sense of the word) Joe Cook, along with another former Amylin CEO Ted Greene and Vaughn Bryson, a former Lilly CEO – that alone must be fairly unusual, but then throw in the stellar MDs other healthcare leaders – killer. We imagine they are all just considering the stock price and smiling ruefully, envisioning a day a few months or a year from now when people will look back and wonder how the stock could've been in a straight or downward sloping line for so long. As always, “we don't comment on stock prices, that's why we left Wall Street,” but ... this one does raise our collective eyebrows. A few other call grace notes: 1) Byetta's room temperature storage indication is expected to be approved in 2H07, which we see as a meaningful advantage given that many doctors (more so than patients) see the lack thereof as a drawback; 2) results of a monotherapy trial will also be available on 2H07 and will allow Amylin to file for a monotherapy label expansion - we view this as a very meaningful advantage that will enable Byetta to be used earlier. While Januvia is a very useful drug in our view, its lack of relative potency suggests it is best used for patients with A1c's below 7.5% - a relatively small part of the population. Byetta could be used far more, in our view. 3) Lilly will be launching Byetta in the EU in 2007. 4) Symlin should receive a pen approval and label expansion to patients on basal insulin alone in 2H07. As Dr. Irl Hirsch said in a recent interview with DCU (see his interview in this issue), some of his patients won't consider Symlin until the pen is available. 4) Albeit early data, Amylin will be reporting on four clinical trials in the INTO program for obesity this year:
 - Pramlintide in combination with phentermine and sibutramine is in phase 2b. This is intended to show the additive effects of the drugs. We were actually kind of surprised that sibutramine is part of the pramlintide study strategy since it doesn't receive raves as monotherapy and has so many rough side effects.
 - Leptin and pramlintide proof of concept study to investigate the synergy seen in preclinical studies. This will be an important report.
 - Pramlintide and PYY safety study. If this combination shows potential it will facilitate triple combination studies with pramlintide, PYY and leptin. This combo excites us the most by far.
 - Second-generation amylinomimetic phase 1 study – these results may come the soonest (before July) and though it's early, promising results would be extremely exciting, particularly for obesity

potential.

- **Merck 4Q06—Januvia sales at \$42 million for less than a full quarter:** For context, we note that first quarter Byetta sales were \$18 million and the second full quarter was just shy of \$50 million. We are partly pointing this out to highlight the amazing Merck figure but also to say that Byetta's early target market of diabetes specialists is an apples and oranges comparison to Januvia's additional target of primary care. But still...we were impressed, given stories we've heard from doctors who were given prodigious sample supply (two months of samples per patient in some cases), which we assume would've also delayed revenue from such patients. Now, just how much stocking was included is a question – we assume a fair amount. Still, this bodes well for the class, as long as no safety concerns emerge, and we're particularly interested to see how the Januvia/metformin combo Janumet does with patients and payers – at the very least, Merck gets another launch, which given the first round, should be a real positive. Of course the question of reimbursement remains all-important; Merck stumbled around regarding Januvia's formulary tier – we believed it to be primarily Tier 2 and 3, but during the call management said 1 and 3, then 1 and 2, then 2 and 3. We still aren't sure but find it hard to believe that an almost \$5 per day medication launched weeks ago could land on tier 1 so soon. But if Merck made it onto one tier 1, we would agree bragging rights are warranted. CFO Judy Lewent noted that Januvia's strong launch reflected the compelling prescribing information for Januvia, early availability in pharmacies, rapid initiation of educational activities to patients, physicians, and payers, and wide reimbursement. As an example, Express Scripts, with 50 million lives, added Januvia in January to its second tier unrestricted formulary. Regarding physicians, she said that Januvia has been well received by both PCPs and endos, which we continue to hear as well and which doesn't surprise us. We think the success will be based not really on how many starts but how many people stay on it how long – as such, we will be very interested to see how durability and real-world drug potency play out. Rather off the cuff, Merck said half of all endos have prescribed the drug to date, which we found impressive – a sign of Merck's marketing power. Management said the initial data suggest that prescriptions were distributed across new, add-on, switch, and continuing patients. Too, Lewent said Januvia has been distributed across disease severity – the drug has been used in monotherapy, in combination with one or two other orals, and with insulin – the last is surprising, since the label doesn't support this, and we would be surprised if use with insulin were reimbursed. Management did not discuss Merck's pipeline though of course Janumet (MK-0431A) is at FDA now and seems prime for an approval sometime soon as noted.
- **Wyeth 4Q06—No diabetes news of note:** Management reported 4Q earnings Jan 29 and mentioned diabetes as part of a long list of discovery programs in promising therapeutic areas. We note that the list pretty much encompassed every large disease state except cancer: diabetes, cardiovascular disease, sepsis, stroke, and Alzheimer's.
- **Bristol-Myers Squibb 4Q06—Details on diabetes collaboration with AstraZeneca:** Management shared some detail on BMS's collaboration with AstraZeneca (AZ) in the company's Jan 25 year end earnings call. The global partnership, first announced Jan 11, is for the development and commercialization of saxagliptin, a DPP-4 inhibitor, and dapagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor. So both investigational compounds are for type 2 diabetes. In the call, management held this collaboration up as an example of the company's strategy to search for partnering opportunities, especially in primary care. Details given during the Q&A include the fact that all costs and revenues subsequent to development will be evenly split, though AstraZeneca would bear about 75% of the development costs. There are currently no change-of-control provisions. When asked "why AstraZeneca," BMS responded that AstraZeneca represents a strong partner with strong commercial capabilities, and its experience in the European market is seen as a key asset that makes it an "attractive partner." Strategically the deal makes sense 1) for BMS, since it has more specialty sales forces now (and forces that focus on high prescribers) and AZ has a big primary care sales force

(same reason BMS went with Merck for muraglitazar); and 2) for AZ, since it wants to do more in diabetes/metabolic/cardiovascular even though it announced in 2Q06 that it was dropping Galida, its dual PPAR, as well as AZD1092, another diabetes compound - the rest of its metabolic pipeline only had pre-clinical and phase 1 compounds. BMS will show data on saxagliptin at this year's ADA - no skin toxicity has been observed to date. In its Jan 11 press release, BMS said it will submit saxagliptin in the first half of 2008. It's unclear how they will differentiate this compound versus Januvia and Galvus, but we assume going forward with AZ gives them more confidence. Regarding dapagliflozin, see below for our primer on the SGLT2 inhibitors, which are being discussed by companies because they prevent the kidney from reabsorbing glucose, thus causing loss of glucose into the urine.

- **BD 1QFY07—Byetta and Lantus drive pen needle growth in slow quarter for US sales ~ CCS now owns Logic BGM line:** Management credited Byetta and Lantus for pen needle growth in the Q&A session of BD's Jan 25 earnings call. The impact of LAR is unknown as yet. In the call, management reported global revenues of \$169 mm in the December quarter (FY ends September), up 3% over last year. In the US, sales were \$90 mm, down 1.1% over last year; sales outside the US were \$78 mm, up 9% over last year. BD's blood glucose monitoring (BGM) product line has been sold for \$20 mm, which we were very surprised wasn't just a bit higher based on IP and revenue though obviously industry and brand difficulties have been well documented. BD netted a pre-tax gain of \$15 mm. BD has classified the BGM line as discontinued operations, with quarter and year results reflecting this fact. During Q&A, management said that it sold the BGM line to CCS Medical. Based in Florida, CCS specializes in home delivery of supplies for chronic conditions and is owned by Warburg Pincus. CCS is an interesting home for the company, especially at that price; in our view, a convergence of forces make diabetes mail order an excellent business: 1) Environmental, genetic and population factors all contribute to patient growth; 2) Mail order is receiving greater attention from industry/government; 3) New products contribute to future product growth; and 4) mail order stands as the fastest growing channel. Additionally, their core focus, pumps, is set to undergo what could be a very promising paradigm shift for these distributors. On the other hand, there are also a number of barriers to success for any BGM business, as BD identified, including 1) Medicare Modernization Act; 2) increased customer acquisition pressure; 3) pricing pressure has increased in blood glucose monitoring and will likely will increase; 4) diversion of product remains a worry (though more to manufacturers than to mail order); 5) Development of products that make blood glucose monitoring unnecessary has intensified; 6) further risk of decline in reimbursement for blood glucose monitoring (e.g., Byetta, Januvia, etc.)
- **Abbott 4Q06—Confidence despite slow BGM market; Navigator approval soon:** In Abbott's year-end earnings call on Jan 24, we learned that Abbott Diabetes Care (ADC) grew a modest 6.5% for the year, in the same range or slightly better than LifeScan's 4-5% estimated organic growth though from a lower base. As just mentioned above, the outlook for the BG monitoring space is not as sunny as it has been in years past - the market is only growing in the mid-single-digits - but Abbott hopes to steal share from competitors and return to double-digit growth in 2007. It has been successful with this strategy in years since the ADC acquisition. Global full-year sales for ADC were \$1.136 billion, up nearly 7% from 2005, while sales in the US were \$547 million, up 5%, and sales internationally were \$589 million, up 8%. Global 4Q sales were \$290 mm, up 1.4% from last year, while US sales were \$135 mm, down 2%, and international sales were \$155 mm, up nearly 5%. Management said Navigator approval is "months" away, so we may see an approval this quarter. This was a slightly more modest timeline than comments earlier in January at the JP Morgan conference that suggested approval in February. COO Rick Gonzalez noted that the FDA had questions about how problems seen with other CGM devices on the market may concern Navigator. A Children with Diabetes (www.childrenwithdiabetes.com) poll plainly shows this week that despite these problems, the majority of voters (over 40% - these polls routinely have over 500 voters) just want reimbursement with an integrated pump/sensor as a close second. Abbott said it responded to FDA

questions around early December and believes that the FDA now has everything it needs for approval. Management also said that approval is pending the inspection of two manufacturing facilities, which they expect will happen “soon.” The launch in March 2006 of Freestyle Freedom was one of the 2006 Abbott milestones mentioned in the call. In diabetes care, Gonzales mentioned a few projects to anticipate: 1) Abbott continues to work on developing a fully integrated glucose testing system, with lancet, meter, and test strip all in one device; 2) Abbott will continue to update the Freestyle and Precision lines in 2007 and that will be launching a new discrete meter device in 2H07 – the smaller, faster Titan, requiring a smaller sample size – which Gonzalez said would pick up a couple of market share points. At the JP Morgan conference in early January, we learned about the Kos acquisition and the Aviator. The Kos acquisition expands Abbott’s presence in the \$20 b dyslipidemia market with Niaspan, a product for raising HDL, and products for LDL and triglycerides. It also includes an inhaled insulin program in phase 2. The Aviator pump, approved a year ago, is in commercial and strategic discussions and a possible partnership is in consideration.

- **J&J 4Q06—Very good LifeScan performance and a foray into diabetes pharma:** In J&J’s Jan 23 year-end earnings call, CEO Bill Weldon emphasized continued strength in the diabetes business, which we think suggests a desire to expand its presence in the field, especially on the pharma side. Management credited Animas and the OneTouch Ultra for LifeScan’s performance – up 15% worldwide over last year’s fourth quarter and up 9% for the year. We believe that while the Ultra2 and the UltraMini have been very well received and represent fabulous additions to the portfolio, Animas would have accounted for the majority of LifeScan’s growth and that organic growth was closer to 9% for the quarter and 4% for the year. In 4Q, US sales in LifeScan were \$289 million, up 12% from a year ago while international sales reached \$253 million in 4Q, up a strong 18% from a year ago – this result marks the first quarter-million sales mark for LifeScan for international sales. Total LifeScan sales reached \$542 million for 4Q, up 15% globally from a year ago. Excluding Animas, we believe LifeScan growth was 9% for the quarter globally (up about 4% in the US and 14% internationally). Full-year 2006 sales for LifeScan reached \$2.1 billion globally, up 9%, with \$1.15 billion in the US, up 10% from 2005 and \$928 million internationally, up 7% from 2005. Excluding Animas, we believe organic LifeScan growth would be closer to 4% both domestically and internationally. We stress that since Animas doesn’t report separately, our estimates are estimates only. J&J also said it will continue working on the closed loop - we perceive this as more validation for the continuous monitor (we assume if they weren’t happy with progress, they wouldn’t mention it) – this is a positive for Abbott, DexCom, and Medtronic in our view. Notably, Weldon said during Q&A that J&J intends to stay very strongly behind the diabetes business. He mentioned the Ortho-McNeil collaboration with Metabolex on developing two new insulin sensitizers, and we assume if this was scripted, this is a partnership J&J is intent on developing and putting resources behind. Good news for them, since strength in diabetes pharma would begin to help fill a gap at the company. As a reminder, the two new pharma compounds are being developed by Ortho-McNeil and Metabolex resulting from their partnership announced last June. The first, MBX-102/JNJ-39659100, is a partial PPAR-gamma agonist/antagonist in phase 2 that acts as an insulin sensitizer – it is said not to cause the weight gain and edema associated with TZDs, and to have equal or possibly greater anti-inflammatory effects, which are a large part of its mechanism for lowering glycemia. MBX and JNJ plan to complete their phase 2 studies in 4Q07 with an end-of-phase 2 meeting with the FDA planned for 1Q08. We will be most eager to see how potency of the new J&J compound emerges. The second compound, MBX-2044, is the second-generation more potent version of the insulin sensitizer, and is now in phase 2a. See our article on inflammation below (page 22) for a more detailed look at these two drugs. Asked about J&J’s anticipated response to GE making a foray into diagnostics, Weldon said that it would only change one competitor to another, and that one area J&J won’t move is diabetes monitoring.

- Pfizer 4Q06—Hurdles admitted for Exubera, peak sales of \$2 billion expected later than hoped:** At Pfizer’s Jan 22 analyst meeting, management suggested hurdles for Exubera in 2006, saying that scaling up manufacturing and educating the market took more time and resources than they had expected – even with the intentionally phased launch. While management believes Pfizer has gained an “understanding of the drivers in the market” and still believes in a \$2 billion peak sales figure for Exubera, they don’t expect to reach that goal “as early as hoped” – originally it has been cited as 2010. We aren’t surprised to learn that building an inhaled insulin market is taking more time than expected. The 2007 strategy includes direct-to-consumer communications, expected to begin in 2H07, and a “focus on market drivers.” Q&A responses reflected Exubera’s weak start – negligible sales in 2006 were due, management said, to the phased launch. No real goals yet to expand internationally, as there will need to be different trials targeting European “one-payer” systems (one such trial will report in mid-2007). See top diabetes blogger Amy Tenderich’s fascinating website www.diabetesmine.com for a very interesting interview with a patient that is positive on inhaled, a few months in! N=1, but an interesting n...
- Innocell—FDA gives go-ahead for phase 2 trials on foot ulcer treatment:** Innocell announced Jan 22 that the FDA had approved its IND application for a phase 2 study on CollaRx Gentamicin, a topical collagen dressing and antibiotic for the treatment of mildly infected diabetic foot ulcers. The technology consists of a biodegradable collagen sponge that releases gentamicin, an aminoglycoside antibiotic, into the wound upon application. The product is already approved as a surgical implant for treating or preventing post-surgical site infections in Europe and other non-US territories. There are currently no topical antibiotics marketed specifically for diabetic foot ulcers in the US. The phase 2 study would compare CollaRx Gentamicin with an oral antibiotic. We’re always eager to see new products for complications and will be watching the efficacy of this therapy in further development.
- Medtronic—Continued commitment to closing the loop:** At Medtronic’s Jan 19 analyst meeting in New York, Chris O’Connell, the new head of MiniMed, gave a terrific talk on the past, current, near term, and long term future of MiniMed. While MiniMed has worked pumps in the past and integration of pump and sensor in the present, in the near-term future the company will be working on the next generation Paradigm pump, semi-automatic insulin dosing capability (this would be fabulous), and enhanced data management. In the long term they continue to develop automating capabilities for closing the loop. O’Connell mentioned STAR 3 (a heavy-duty trial comparing the new sensor-pump combo, the 522/722 against the gold-standard MDI – Lantus and rapid acting analogs) and announced they had had the first enrollment the week prior. He also discussed the importance of data management and sensor augmented pump and automated dosing and said a semi-closed pump would happen by mid to late 2008 (calendar, not fiscal). He laid out plans for products after that to have continuous iteration, leading to an automated external insulin delivery system. In a broader talk, Medtronic President and COO Bill Hawkins announced that the “new” Guardian RT would be available by end of the fiscal year, which ends in April. This wasn’t presented as a delay as such, but we think this had originally been planned for end of calendar year and then by end of this Jan. The biggest positive takeaway in our view was hearing about the size of the transmitter for the next-gen combined sensor-pump, which sounds significantly smaller. On market development, for diabetes, Medtronic estimates the insulin pump market at \$1.2 b globally and says the total market potential is \$4.8 b (they must assume almost total type 1 penetration). They say the disposables’ business problems are resolved at end of FY06 and that disposables will now contribute to growth, now that the oversupply has been addressed. CEO Art Collins mentioned there have been process improvements and changes in diabetes resulting in greater efficiencies in diabetes selling costs. On the obesity device front, things are quiet. There was a clear negative vibe about Transcend, the implantable gastric stimulator that is part of Transneuronix, which Medtronic got with its \$260 mm acquisition of Transneuronix in mid-2005 (negative news on trial came in Dec 2005). Dr Richard Kuntz, who oversees neurological businesses (of which obesity is a part) said there remained great

interest in stomach stimulation/appetite etc., but this was tempered by his admission that they are looking mostly at pre-clinical research right now and said they may launch another study “in the next year or two” – so no time soon. Although the Transneuronix acquisition doesn't appear positive, we understand milestones had been very high, so deal structure seems smart relative to how it could have been structured. Overall, we thought the day was very successful for Medtronic MiniMed, and they clearly demonstrated they are on the move and there is renewed energy influencing the business.

- **Novartis 4Q06—Galvus launch expected in 1H07, and Galvus/metformin in 2H07:** Expectations for Galvus were managed carefully at Novartis's Jan 18 year-end earnings call, where Galvus's expected launch date was written as 1H on a presentation slide. As a reminder, Novartis announced on Nov 13 that Galvus had been put on a three-month regulatory delay after the FDA requested more data after studies showed skin irritation in monkeys. In the year-end call, it sounded like this may be stretched a bit – likely just playing it safe. Also on the same slide was a metformin combination expected in the second half of the year. Overall, there was little discussion of Galvus or diabetes at all. Management referred to the addition of 1,000 sales reps, originally announced in the Q206 call as preparation for the expected launches of eight drugs in 2007 (including Galvus). They mentioned that they were watching Merck and its sales force closely. We think that a Galvus/metformin combo will be important, since payers may be less likely to cover DPP-4 inhibitors in metformin-naïve patients. The question is whether patients have to fail on metformin first. In contrast to the 40% of patients who had GI problems on metformin in ADOPT, early reports on DPP-4 inhibitors say that their side-effect profiles are like placebo for most patients.
- **MicroIslet—Generous chairman to lend \$2 million in capital:** MicroIslet announced Jan 16 that John Hagenbuch, Chairman of its Board of Directors, has agreed to lend the company \$2 million in cash. Hagenbuch will receive a one-year unsecured promissory note and simple interest at the prime rate published in the Wall Street Journal, as well as a 10-year warrant allowing the cash purchase of up to 500,000 shares of stock at an exercise price of \$1.00 per share. MicroIslet held a pre-IND meeting with the FDA in December regarding its technology for the transplantation of microencapsulated porcine islets into people with type 1 diabetes. MicroIslet continues to have a very troubled existence; on Jan. 30, the American Stock Exchange sent a letter to the company stating that MicroIslet did not comply with certain listing standards, based on low stockholders' equity, losses from continuing operations and continuing net losses.
- **Genaera—Hoping to enter the obesity pipeline with trodusquemine:** Genaera presented preclinical data at the Keystone symposia on Jan 16 on its obesity drug candidate trodusquemine (MSI -1436), a selective protein tyrosine phosphatase inhibitor. In animal models, trodusquemine suppresses appetite, induces weight loss, and helps normalize blood glucose and cholesterol levels. CEO Jack Armstrong indicated that Genaera hopes to begin phase 1 studies in 1H07.
- **Lilly/Alkermes—Expansion on inhaled insulin partnership:** In the new agreement, announced Jan 8, Alkermes will be Lilly's exclusive commercial manufacturer for AIR Insulin powder. Lilly will construct and operate a second manufacturing line at Alkermes' commercial-scale production facility in order to expand post-launch production capacity. It looks positive that Lilly remains committed enough to the potential for inhaled insulin to ink an agreement with Alkermes for a second manufacturing line for AIR, Lilly's pulmonary insulin using Alkermes drug delivery technology. We think the arrangement looks pretty similar to what Nektar has with Pfizer - no interesting details regarding financial terms or manufacturing capacity.
- **MacroGenics—JDRF to fund a drug that can slow type 1 progression:** On Jan 3, the JDRF announced a partnership with MacroGenics, a biotechnology company that focuses in part on autoimmune diseases, to develop a drug to slow the progression to type 1 diabetes in new patients.

The drug is an anti-CD3 antibody called teplizumab that interferes with the T cell attack on islets. JDRF will provide up to \$2 million to fund the “Protégé” phase 2/3 clinical trial as well as follow-up studies at Yale by Dr. Kevan Herold. The trial tests three dosing regimens in children and adults and is designed to test safety, tolerability, and efficacy in reducing insulin requirements. Dr. Herold’s June 2005 *Diabetes* paper showed improved A1c, improved C-reactive peptide response, and reduced insulin needs over two years in 21 subjects treated with the drug compared to controls. This partnership is part of JDRF’s Industry Discovery and Development Partnership program, and Protégé is one of the first phase 3 trials JDRF has funded.

<http://www.clinicaltrials.gov/ct/show/NCT00385697?order=1>

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

2. Interview with Dr. Irl Hirsch

Irl B. Hirsch, MD, is Professor of Medicine at the University of Washington School of Medicine and Medical Director of the Diabetes Care Center at the University of Washington Medical Center. Dr. Hirsch has authored ~ 100 original papers and over 40 abstracts as well as dozens of letters, editorials, and book chapters. In addition, he has published books on diabetes care geared toward both physicians and patients. He was named ADA Clinician of the Year in 2005, received AACE’s Distinguished Endocrinologist award in 2006, and he has been repeatedly recognized for his clinical excellence. He sits on the Board of Directors for the ADA, JDRF, and the American Board of Internal Medicine. The former associate editor and editor-in-chief of Clinical Diabetes, Dr. Hirsch is currently the editor-in-chief of DOC News. He recently discussed with us his latest thoughts on continuous glucose monitoring and glycemic variability, incretins, inhaled insulin, and how diabetes care in America is in a relative state of crisis.

Kelly: Thanks so much for talking to us, Dr. Hirsch. We’d love to start off by getting your take on continuous glucose monitoring. Is it ready for prime time, in light of questions regarding quality and reliability and reimbursement? Is it too much information, too little, about right ... or is that a ridiculous question in light of patient heterogeneity?

Dr. Hirsch: We’re in the early days. First of all, nobody really has ever taught health care professionals—much less patients—what to do with the information. If you have a continuous graph, what do you do with the glycemic profiles, especially if you are a patient? That is, you may see your current blood glucose is 95 and you know that a half hour ago your glucose was 135, and now you’re getting ready to eat, and now you would normally give 8 units for what you’re eating, but your blood sugar is dropping quickly. How much less insulin do you take? How do you change the lag time? You know, usually you take your rapid-acting insulin, you wait a few minutes before eating—eating nothing may be dangerous in this case. We’re going to teach patients how to interpret—that’s the goal. We have to recognize that some clinicians can’t or don’t even teach patients how to do the finger stick interpretation. First things first—baby steps are required.

Kelly: For both the technology and for clinicians’ time, what sort of outcomes data would increase prospects for reimbursement?

Dr. Hirsch: It needs to be based on studies showing which data works best for large numbers of patients. It may be that we will need different types of software for different patient populations. In the world of SMBG, little attention was paid to data interpretation for lots of reasons, the main one being physicians saw this as being too labor intensive. I believe that one of the positive aspects of CGM is it will show both physicians and patients how powerful this tool can be, and it likely will increase use of downloading old-fashioned SMBG meters. The other good news is that the companies are putting more time into thinking about their software for downloading. Still, we need studies to guide us as to what is best.

Kelly: Seems like there's got to be a code for continuous monitoring to be reimbursed – and there will be the coverage battles - but before that, there must be evidence and there must be indication from the clinicians that patients want to use the products. But it's hard for patients to want to use the product if it isn't reimbursed, to say nothing of the problems with any first-generation device.

Dr. Hirsch: That's the problem, what's the chicken and what's the egg? We need to all remember they are first generation and they will all improve. Obviously, they are not yet perfect, but for people who understand how to use trends in addition to SMBG, our initial experience has been great. For me, I can't wear the Medtronic as for some reason I get inflammation with their sensor. In my STAR1 study, no one had that problem, so I must be unusual in that regard. Clearly, no one has software as good as the Medtronic Carelink, but to be fair, I haven't really had enough experience with the Abbott software to make a good comparison. DexCom does not have all of the bells and whistles literally, but for me that is a good thing. I look at my sensor constantly, so having it alarm all day would just be an annoyance. The arrows one gets with the Abbott and Medtronic are great benefits, and hopefully we will see something similar in the future from DexCom. For me, and my wife will agree – I won't sleep or leave the house without wearing it..

Kelly: The million-dollar question – actually I suppose it's possible this could ultimately be a billion dollar question. When do you think we'll see a reimbursed real-time continuous glucose monitor?

Dr. Hirsch: CGM is a very, very small market with no reimbursement right now, as you know. There is already all the paperwork to do with pumps, so I think that even when reimbursed, CGM will put so much more burden on the doctor and the doctor's staff. We figured in our clinic, it costs us 10-15% of medical assistant's time just for the administrative burden for pumps! New technology will make the amount of paperwork worse unless someone realizes this is the rate limiting step of using newer, better technology. What I'd like to see is a more streamlined process that won't scare so many doctors (and patients) away from these better tools.

Kelly: Switching gears, you've done a huge amount of interesting work looking at inpatient insulin use. This relates to a theme we've been thinking about a lot lately, namely, the costs of diabetes continue to skyrocket. Everyone says “yeah, yeah...” but I'm wondering if you can talk about your focus on inpatients because *this* of course is where the poor outcomes and the costs are – over 40% of the \$100 billion – plus in direct costs relates to costs in the hospital. And the vast majority of the costs surround complications rather than treatments, right? The work done for the ACE/AACE Consensus Conference on Inpatient Glycemic Control implied that we could reduce inpatient costs through better glycemic control; a year later, we wonder if you are optimistic that this can happen?

Dr. Hirsch: I actually think that over time it will get better. It will not start in medical units; it will start in ICUs. My surprise in going around the country is that very few hospitals do insulin on the floors; they use a subQ sliding scale. I recently asked a group of 120 endocrinologists about whether they did sliding scale insulin in their hospitals, and about 80% raised their hand. Nurses won't let them do intravenous. What will get people to change will not be guidelines. What will help is if anesthesiologists and cardiologists take more ownership and later publish. I'm excited at how interested the hospitalist group (Society of Hospital Medicine) have seen this as a major priority. .

Kelly: Certainly, the evidence is accruing. Dr. Tony Furnary has shown with the Portland Protocol that hyperglycemia is a casual factor for death, infection, and length of hospital in diabetic patients. And, as you say, Dr. Grete van den Berge's ICU studies further showed that intensive control of glycemia with intravenous insulin improves mortality and morbidity in intensive care patients who may not even have diabetes but who have stress-associated hyperglycemia. At AADE last year we sat in on an inpatient talk where the educators were all just adamantly opposed to sliding scale, but hospital administration was a big barrier because of the cost of intensive management. What else will change this?

Dr. Hirsch: One, if the Joint Commission on Hospital Accreditation (JHACO) came to a consensus about this, or two, if there is a bad outcome and a lawyer gets involved. I know of one hospital where there were two deaths from sliding scale, both from hypoglycemia. In that hospital, they have not changed the way they manage people with diabetes, but if and when a lawyer is involved...

Kelly: Thinking about relatively new drugs in your armamentarium, we have seen over the last 18 months that two new injectable drugs, Symlin and Byetta, are generating a lot of interest for type 1 and 2 patients respectively. How widely are you prescribing these new drugs and what has your experience been?

Dr. Hirsch: Quite a bit for both. Symlin is tricky as we have learned that only those sophisticated with their insulin use it long-term. The three-times daily dosing with the old-fashioned syringe is a turn-off for some, but those who do well with it don't want to come off of it. A lot of these patients need a lot of hand-holding the first month or two, so providers need to know about that. The pen coming out this year should help. In fact, I have several patients (mostly on pumps) who don't want to even try Symlin until the pen is available. Byetta seems to cause more nausea than Symlin, and most of us have had great success using it with basal insulin . . . but new type 2 patients when talking about what drug to start often decide to take Januvia simply because they don't want to deal with the shot or shots and the hassle of keeping it cool. It is sort of like talking about insulin 20 years ago. The hardest thing is going from no shots to one shot. Going from 1 shot (basal insulin) to 3 shots (with Byetta) is not a big deal.

Kelly: What do you think of the idea of Byetta being tested for use in pre-diabetes?

Dr. Hirsch: My guess is Byetta would be a tremendous agent for pre-diabetes. The key would be if the beta cell benefits are true in humans like we think they are, this could be a big hit. The weight loss and the reduction of postprandial glucose levels may make this a homerun for this population. BUT, if the B-cell benefit is real, what about Byetta (or even a DPP-IV) for preclinical type 1 diabetes?

Kelly: Very exciting prospects. Moving to another new product, inhaled insulin-Exubera made a big media splash when it was introduced, but patient interest and acceptance appear so far to be mixed at best. What is your view of this drug and on inhaled insulin more broadly?

Dr. Hirsch: Inhaled insulin may be great for some patients, but it obviously doesn't appear the market is ready. My take is that the insulin will need to be easier to administer than the Exubera is, and the insulin will require some type of pharmacokinetic/pharmacodynamic advantage. That is why I think both the Lilly preparation and the Mannkind insulin will do better.

Kelly: It will be a few more years before those come to market... For now, what is your philosophy on insulin for type 2 patients?

Dr. Hirsch: First, I give only prandial if the patient will accept that, or if they have an A1c of greater than 10%, I start both. In terms of insulin on the clinical front, there's good news and bad news. It's a shame that the DCCT wasn't translated into clinical practice better than it was. But we're doing a better job. Multiple injections may be more important than A1c because of the protection offered by controlling glycemic variability. The old thinking was that if we could get away without more shots, it would be better, but the exact opposite may be true.

Kelly: Now that Byetta has been out nearly two years, we'd also love to hear what you think Byetta and other GLP-1 therapies will do to demand for insulin?

Dr. Hirsch: Insulin is still the cornerstone of all of diabetes therapy. It may be that like with the introduction of troglitazone 10 years ago, the greatest impact on insulin growth will be the DPP-4s since they are oral and much easier for the primary care physicians to prescribe. The field is becoming so crowded so fast, that many are finding it difficult to keep up with all of these new choices. The added choices are a good thing, but to keep A1C levels within target (which as a group we have not done very well with) insulin will still be required. To me, the real question is what happens after many years of some of these newer therapies (like Byetta) that may have B-cell preservation qualities? Perhaps that will alter the insulin market, or if pay-for-performance really is a major factor, perhaps we would be using more insulin with Byetta, assuming there is a label change some day. Too hard to know as there are too many unanswered questions, but at the very least it seems to me there will be many reasons to be more aggressive with diabetes care.

Kelly: How willing are type 2 patients to take shots?

Dr. Hirsch: If you look at the national data, it's interesting, there are more type 2s taking three and four shots a day than *ever* before. So there are some trends showing that we're seeing more MDI [multiple daily injections] in the type 2 population, but it's a very slow pick-up. There are still big problems with the type 2 populations and how they are treated. Say an average doctor wants to get patients' A1c down into the 6% range. They can do that with Lantus if they start them on insulin when their A1c is 8%. But when they're starting with an A1c of 10%, you know that if they start the Lantus without another insulin, they are not going to reach goal. They're probably going to need more shots. And if you're a type 1 and you don't know any different, that's fine. But for a type 2, it may not fly.

Kelly: How has this changed with the introduction of Byetta, and what does that mean for inhaled insulin?

Dr. Hirsch: Depends on who the physician or the diabetes nurse educator is. I have found it is the way the therapy is presented to the patient. If the HCP is negative against the shots, this will come across to the patient. Certain ethnic groups also seem much less enthusiastic about injections.

Kelly: That certainly reminds me of the old problem of patient-initiated care. For all the tools and technology that we have, patient motivation is still critical for effective management. How do you motivate your patients?

Dr. Hirsch: This is very difficult. I feel I spend a lot of my time as a cheerleader. Some patients do better when family members are involved (and some do worse!). Some do better when writing things down, while others seem to be motivated more with weekly downloads. The biggest problem I see (probably worse in Seattle) is those patients who fail due to depression. Mental illness is a huge problem that often gets overlooked by both patients and physicians. If I see a college graduate, or maybe someone with less education but has done well with a pregnancy, and we download the meter and I see less than two checks daily, my first guess is I am dealing with depression, often not yet diagnosed. So this is a huge issue, and it's the reason we have a psychologist and psychiatrist in our clinic. When the depression is adequately treated, many (but not all) of these patients do better.

Kelly: But it's sad to say, most diabetes clinics don't have that luxury, and with limited resources they're even further hampered by the fact that diabetes care delivered via the telephone or Internet is not routinely—or ever—reimbursed.

Dr. Hirsch: There's a real reimbursement problem in this area, as you say. Basically, we're in the office at 8 o'clock at night working for free. That's the problem. It's ultimately just not affordable – that's why so many endocrinologists have left the field.

Kelly: And because there's no reimbursement, that reduces further the number of CDEs, which makes office visits even less productive.

Dr. Hirsch: The reimbursement for nurses and nutritionists and behavioral scientists, if anything, has gone down in the years since the DCCT was published!

Kelly: It seems clear that patient outcomes would improve with better and easier access. We all know that most of the costs of this disease are associated with chronic complications, not with treatments. How can access be increased?

Dr. Hirsch: Industry probably has some clout. Every state I talk to, everyone is fighting for their lives to try to keep the little bit of coverage they have now. One can't even pay salaries with the kind of coverage that is available in most states.

Kelly: There is great concern about the shortage of endocrinologists. Where do you see this heading?

Dr. Hirsch: If you look at who is going into the endocrine programs today, those programs are much different than 30 years ago. Then, they got the smartest and brightest people from internal medicine classes. Today, those people are going into cardiology, GI, and pulmonary. There, you get reimbursed for procedures. Right now in pediatric endocrinology, there's truly a crisis. It's very discouraging overall and, actually, as passionate as you are about diabetes, where are you going to get your care 20 or 30 years from now? I worry that 20 years from now, we are not going to have endocrinologists. Nobody is coming in to take the place of the people who are retiring. There is no financial incentive to do it right now.

Kelly: This is a disaster.

Dr. Hirsch: It is a disaster.

Kelly: On another matter, what do you think of the smart pumps? Good or bad for patients, overall? And Insulet's disposable pump?

Dr. Hirsch: In order of the question: good, good, and I like it a lot. The thing about smart pumps, is that I would call them "smarter" since they don't take into account glycemic trends. For that you need a smart patient doing a lot of SMBG or a rt-CGM, knowing when to over-ride the pump recommendation. For example, if one checks a BG prior to driving a car, and the BG says "94 mg/dL", we would usually tell the patient to have a small snack. But what if the trend is going up at 2 mg/dL/min. Alternatively, in this same situation before driving a car and the glucose was "130 mg/dL" and the trend was now going DOWN at 2 mg/dL/min, one might want a snack before an hour-long ride in rush hour traffic! So these nuances need to be understood about smart pumps. And OmniPod is a fabulous pump, I have found especially for young women who up until now did not want to "be connected" to the tubing. I have a waiting list of young women for this new pump as we have not had it available on the West Coast.

Kelly: Bottom line, what do you think is really needed to further build the pump market?

Dr. Hirsch: I think the market would be bigger if the pump companies would do a better job of training doctors, especially training fellows. You know the endocrine fellows in training have been sort of ignored for years. All the insulin companies and I think all of the pump companies are realizing that they have to acknowledge them and acknowledge their presence because these are the guys who would be going into practice prescribing pumps and insulin and expensive oral agents. When you hit them really for the first time once they're in practice it's kind of late; you want to reach them earlier and teach them the therapy.

And so I think what's going to happen is we are going to see more companies teaching pump therapy to fellows as opposed to waiting until they are in practice for a few years.

Kelly: ADOPT really showed some compelling data about the lack of durability with monotherapy. Can you share some of your thoughts on the ADOPT trial?

Dr. Hirsch: ADOPT compared three different drugs in monotherapy: rosiglitazone, metformin, and glyburide. As I recently said in DOC News, the most relevant way to think about the results is that A1c was maintained below 7% for 60 months with rosiglitazone (Avandia), 45 months with metformin, and 33 months with glyburide. So rosiglitazone clearly was more effective *and* durable, particularly against metformin, at least in a well-performed statistical analysis.

Kelly: And sulfonylureas performed the worst. It's interesting that right now the ADA/EASD's drug therapy algorithm for type 2 diabetes recommends initiating all patients on metformin, not rosiglitazone. We assume this is because it's the least expensive drug and it's weight neutral – although it does have side effects. Does ADOPT change the way we should be initiating drug therapy?

Dr. Hirsch: I think not. Let's look at the drug costs. For the agents used in ADOPT, a month's supply of drug cost \$211 for rosiglitazone, \$56 for metformin, and \$18 for glyburide. Comparing rosiglitazone with metformin, do 15 additional months prior to drug failure justify this added cost, particularly since no added cardiovascular benefits have been proven for this population?

Besides, the 6.9 kilogram weight gain [15.2 pounds] with rosiglitazone, compared with metformin, is the fundamental reason I can't recommend this therapy as first-line for this often obese population. We need to look at type 2 diabetes differently now than we did a decade ago, before so many drug therapy options existed. Now there are drugs that are generally weight-neutral, such as metformin, DPP-IV inhibitors, and alpha-glucosidase inhibitors, or even weight-losing like exenatide. These agents must at least be considered in anyone's algorithm.

Kelly: A lot of these drugs also more directly address the issue of variability – the incretins, for example, which only stimulate glucose-dependent insulin secretion. You have said in the past that too much emphasis is placed on A1c control and not enough on keeping all blood glucose values as close to normal as possible. It seems this view is finally starting to move into the mainstream among doctors and nurses. What prompted your initial interest in this area?

Dr. Hirsch: When we started downloading data about 10 years ago, I realized that our gold standard of A1c wasn't enough, and I also realized that looking at simple averages didn't give me the whole picture. I saw that I could get much more meaningful information by evaluating standard deviations [glycemic variability from normal glucose levels]. It all started with an amazing software program from LifeScan that had time-specific standard deviations. I realized that I could look at a download and see who was making smart choices about insulin dosing, who was testing more between meals, and who was in optimal control.

Remember, one big issue here is that typical logbook data leaves out a lot of information. Patients leave out significant pieces, sometimes consciously, sometimes unconsciously. With the download you get everything, which you see in both the averages and standard deviations—both critical tools.

I think that a lot of people are embarrassed about the pizza and the beer that they had on Saturday night, and they don't want their doctor to see that 435 mg/dL (24.1 mmol/L) blood sugar . . . [but] I see the 400-plus blood sugar when I do the downloads, and that's good data for me. When I see a standard deviation

that's way out of whack, when I see certain times of day when the averages are either too high or too low, I can focus on that. When you have such limited time for office visits as we do, you need to learn how to analyze and counsel as efficiently as possible.

Kelly: What made you believe that glycemic variability was important for a patient's overall control?

Dr. Hirsch: It started with a report from the DCCT study group in 1995. As you recall, patients in the intensive therapy arm were mostly taking mealtime regular insulin and basal with NPH or Ultralente. They were doing a better job than the conventional group of matching prandial insulin with their food intake. But at *any* given level of A1c, the intensive therapy group had 40% to 60% less risk of developing complications. So if you had an A1c of 8%, or even 9% in the intensive therapy group of the DCCT, you had at the very most an 8% risk of retinopathy, whereas people with the same A1c in the conventional therapy group had a 20% risk of retinopathy.

Kelly: So you would say that intensive therapy, even as control inevitably worsened after the trial, was still found to be protective?

Dr. Hirsch: Yes. But it's not that simple. Everybody interpreted the DCCT as an A1c study. But since then there have been some epidemiologic studies that show positive results from focusing on post-prandial hyperglycemia, such as the Stop-NIDDM study.

There's a group in Italy led by Dr. Antonio Ceriello (now in the UK) that first showed a few years ago that in a cell culture, if you have glucose levels at 90 mg/dl, you get a certain amount of cell death. If you have glucose levels at 400 mg/dl, you get a little bit more cell death. But where you get the most cell death is when you alternate between 90 and 400. You're much better off at 400 than alternating back and forth. It's the variation that hurts, which in patients I measure with standard deviation. This same group went on to show that these up-and-down glucose levels in cell culture generated more of the reactive free radical molecule superoxide, which is thought to be responsible for microvascular complications.

Then Dr. Louis Monnier and his colleagues found that in patients with type 2 diabetes, there is a linear correlation between free radical production and the magnitude of glucose fluctuations, independent of the fasting glucose level or A1c value. This may explain the DCCT findings that diabetic retinopathy is reduced by intensive treatment. The Monnier findings, if confirmed in larger studies, have enormous clinical implications. First, his data suggest that patients with type 2 diabetes should measure their blood glucose more frequently to monitor glycemic variability, regardless of the effect on A1c. Second, the therapeutic strategies now in use should be evaluated for their potential to minimize glycemic excursion, as well as their ability to reduce A1c.

I think that when further studies are done, it will be clear that it's *not* just about A1c. The A1c is important, but how you *got* to that A1c matters too. A related question: why do we see a higher percentage of microvascular disease, eye and kidney disease, in type 1 than in type 2 diabetes? My hypothesis is that type 2s have background insulin around and their standard deviations are lower. You see much higher standard deviations with type 1 patients. The bottom line is that I think we've misinterpreted the DCCT. It all goes back to glucose variability.

Kelly: The Monnier piece in JAMA last year, on which you wrote the editorial, was so compelling. What do you say to the point that randomized controlled trials are needed here? Will that happen? Should that happen?

Dr. Hirsch: What I can tell you is that I think as time goes on, we're going to be looking much differently at how you get to the A1c. I suggested to companies that they do a study on variability, but the problem is that nobody, especially the FDA, looks at that as a reasonable endpoint.

Kelly: It seems like you're talking about whether the quality of A1c alone is sufficient. Should standard deviation become a standard measure of glycemic control in diabetes? It seems like the FDA doesn't consider this currently.

Dr. Hirsch: Nobody does. The ADA, ACE, the NIH, the CDC, everybody's looking at A1c.

Kelly: To really study standard deviation properly would require a long-term outcomes study, where we looked at patients over many years to see if controlling glucose variability reduced their risk of complications, correct?

Dr. Hirsch: Yes, this is all hypothesis-generated.

Kelly: In Dr. Monnier's study, they used continuous glucose monitors to measure glucose fluctuations in the participants. It sounds like it would be in the interest of the continuous glucose monitoring companies to do a long-term outcomes study on glycemic variability. Do you think that industry could work together to do a trial like this or are the costs simply too overwhelming? I know it's easy for me to forget that the DCCT was a 1,440-patient study that cost \$140 million in 1985-1990 U.S. dollars!

Dr. Hirsch: I don't think anybody is ready to repeat a DCCT-type trial. But what I do know is that I don't need a lot of high-tech technology to download a glucose meter. Not only that, but last year Medicare approved a CPT code for Internet office visits. It's probably going to be years before anything happens with that, but now that we can do this downloading and we can read it online, real change could occur. The studies show we can improve glucose control without face-to-face visits. Right now, remember, you can only get paid for face-to-face visits.

Kelly: Which other trials do you think are most interesting right now?

Dr. Hirsch: ORIGIN is a multi-national study of 10,000 people, funded by Sanofi. They are studying early type 2 patients who are on one drug or people with IGT or IFG; to get into the study, people need mild hypertension or documented vascular disease. There are two arms, with one group randomized to glargine and the other to no glargine. They are looking at how insulin is anti-inflammatory. The reality is that it's hard to recruit. The trial is expected to be completed in October 2009. ACCORD is a trial with a goal of getting A1cs to 6, to see if there is a difference between an A1c of 6 and an A1c of 7.5 in terms of cardiovascular outcomes. SEARCH is a great study funded by CDC, trying to find out what kind of diabetes kids have before age 20. They are trying to learn how common diabetes is, and which kinds. There are over 4,000 kids enrolled, including those with antibodies and type 1, those that are very resistant to insulin, those with metabolic syndrome, hybrids. This study will get to the root of it. The upshot from the initial SEARCH data is we are seeing a lot of fat kids with type 1 diabetes, and almost no type 2 diabetes below the age of 10 years old?

Kelly: A couple of burning questions in closing. What aspects of diabetes deserve more research but aren't getting them?

Dr. Hirsch: Translating research into practice is one. How come we have such a hard time? Why do we do such a poor job? Why can't the primary doctor do a better job? Time! We need more research into improving the system. We need more research into prevention of both kinds of diabetes.

Kelly: That's right – we wrote in our December issue that IDF and Lilly were giving some big awards in translational research this year, which translational research expert Dr. Linda Siminerio appeared very positive on in South Africa, so we'll look forward to see what is funded. Where has the most progress been made on the complication front—microvascular or macrovascular and what, in particular?

Dr. Hirsch: I think the major advances have been in gaining an understanding of inflammation. With regards to macrovascular disease, we've learned not only how blood pressure, lipids, and smoking affects outcomes, but we now have a better understanding how all of this is impacted by inflammation. The inflammatory process involves the fat tissue (not good if you have too much of it!), blood cells, and the liver. What this does is it presents potential new targets for treatment. This inflammatory process also appears to impact microvascular disease, but perhaps the process of oxidative stress as noted by Michael Brownlee is more important. What does seem clear to me is that inflammation is co-modulated by glucose and insulin, so an imbalance of one or the other could turn inflammation on. All of this is still in its early stages of understanding, but it is an exciting time as the science unfolds.

Kelly: What small companies on the horizon are interesting to you?

Dr. Hirsch: Certainly I see OmniPod as “interesting” and DexCom has a great product that my guess will only get better. I am also quite interested in the Biodel product of Viaject as this insulin could be a huge advantage for pump patients or even beyond as we get closer to “closing the loop.” Our current “rapid-acting insulins” are simply not rapid enough when one eats a high-carb meal! I am also interested in seeing what the phase 3 data will look like from Mannkind's Technosphere Insulin.

Kelly: We so appreciate your time. You are an incredible credit to the field of endocrinology, and we're so lucky to have had this time with you. Thank you again and all the very best to you from the writers and the readers of *Diabetes Close Up*.

See some of Dr. Hirsch's expanded comments on www.closeconcerns.com along with our extended interview with Dr. Xavier Pi-Sunyer from last issue, in case you missed that.

—by Kelly L. Close

3. The Druggist and the Diabetic: A New Role For A Time-Honored Profession

Let's be honest: no one likes going to the pharmacy. On many visits, the lines are long, the staff is frenzied, and the response to the query – “do you have any questions for the pharmacist?” – is usually a clipped “no.”

But in diabetes, the druggist *should* play a more integral role, if only because the patient has far more encounters with the pharmacist than with the doctor or nurse. How beneficial would those encounters be if clinical care – not just prescriptions – were actually provided?

The answer, it turns out, is very beneficial. A program in Asheville, N.C., which began 10 years ago, has put pharmacists on the front line in diabetes care – and the result has been improved outcomes for patients and reduced health care costs for their employer (the city of Asheville). And now the program, with funding from pharmaceutical companies, is being expanded to employers across the country; it's also receiving national media attention, most recently as part of *The New York Times* ongoing broad coverage on diabetes.

In many ways, the effort simply confirms what was shown in the DCCT (Diabetes Control and Complications Trial) and has been proven in many studies since: sustained intervention by health care providers will benefit diabetic patients and – despite upfront costs – ultimately save money. But the

hurdles to create those kinds of programs – bureaucratic inertia, financial shortsightedness – have been significant. In Asheville at least, they have been overcome.

The program's goal is simple: use the pharmacist to reach diabetic patients early and often so that problems can be detected immediately and effective treatment can prevent the high cost of poor control – be it visits to the hospital emergency room or, down the road, debilitating complications.

“There's a disconnect with the whole health insurance industry,” John Miall, one of the founders of the program, told us. “The whole premise is we pay for sickness. But we have to align financial incentives for wellness. There's a lot to be said for keeping people well. You can buy trainloads of drugs, but that's cheaper than one year of dialysis.”

Miall is now retired, but 10 years ago, as the city's director of risk management, he had become increasingly concerned about the escalating costs of chronic diseases, diabetes the most conspicuous. An acquaintance that ran the pharmacy at Mission Hospitals in town encouraged him to develop a program that involved pharmacists in patient care. Meetings were held with local physicians, educators, and nutritionists, and a plan was developed for city employees who have diabetes.

The key was to create incentives for everyone. The patients themselves would receive free medication for one year (no co-pays) if they agreed to attend monthly meetings with druggists, have their glucose meters downloaded, and submit to regular medical tests (for blood pressure, foot exams, cholesterol levels) as well as blood draws for A1c levels. The pharmacists (but not the drug stores) would be compensated based on specific services. For example, they would receive \$150 for an initial visit (as of 2004, the average cost per visit was \$48). The real question was how much money would the program cost, or save, the city of Asheville. “I couldn't go to [city council members] and say, ‘I found a whole new way to spend money,’” Miall said. “But if it developed positive outcomes, I could make a case.”

With 48 patients initially enrolled in the program, Miall was hoping for positive outcomes in 12 months. He got it in six. Costs fell immediately – primarily because there were fewer emergency room visits. In one year, the city's health-care costs for their diabetic employees dropped from \$6,127 per patient to \$3,554 per year. The success allowed Asheville to waive the co-pays on medicine permanently.

But the long-term cost benefits will be even greater with improved blood-sugar control leading to fewer complications. The program now has more than 120 patients, and their average A1c levels have fallen from 7.6 percent to 6.7 percent, according to the American Pharmacists Foundation, a non-profit. At the start of the program, the average number of “diabetic-sick days” per patient was 12.6 per year. After six years, it was 6.01.

Improvements reflect the value of preventive care. At the start of the program, not one patient was taking an ACE inhibitor for hypertension or congestive heart failure; after 24 months, 57 percent were. Increased numbers of patients are being checked for cholesterol, blood pressure, and foot sores. The pharmacist calls the patient's physician when certain “triggers” are hit – an elevated A1c, for example – and the doctor can see the patient to modify treatment. But beyond medicine, the druggist plays an important role as coach and cheerleader – a role, unfortunately, that many doctors and nurses simply don't have the time to play, but that kind of support makes a huge difference for anyone with a chronic disease.

Miall now consults with the American Pharmacists Foundation, which is trying to expand the program – or, as Miall said, “put it on steroids.” Among other things, it has created a Savings Calculator that breaks down the costs and savings for any employer: For example, an employer with 5,000 employees would have an estimated 2,000 diabetic enrollees, and the first-year investment in the program would be \$529,850. (That includes \$120,000 for pharmacists' counseling and \$120,000 for waived co-pays and

patient incentives.) But the Savings Calculator estimates that the employer would save \$664,560 in reduced hospital admissions, saving the employer \$134,710 in one year.

With grants of about \$1 million from Sanofi-Aventis and GlaxoSmithKline, the foundation is helping to install and replicate the program with about 40 different employers around the country; clients include private companies and municipalities as well as the Ohio State University.

Miall, who was preparing for an interview with a network news show when we spoke to him, said the program can be used for many illnesses – asthma, hypertension, depression, cholesterol, or any other chronic disease. “There are no limits,” he said.

—by James S. Hirsch

4. Conference Report: Keystone Symposia on Diabetes and Obesity

The Keystone symposia bring physician-researchers and scientists together to discuss their work (often still unpublished!) at the Keystone Resort in Colorado... ski apparel recommended. This year, we attended the gathering on diabetes and obesity, which took place January 14-19. More than 600 participants attended the conference, including clinicians, academics, and industry scientists. Below we present our takeaways on some of the major topics.

- **Hypothalamic energy and nutrient sensing** – This was the highlight of the conference. Dr. Luciano Rossetti, an internationally-recognized researcher at Albert Einstein in New York and former director of its diabetes research and training center (now SVP and franchise head of diabetes and obesity research at Merck – see DCU #62) explained that the neurons in the hypothalamus are sensitive to nutrients and hormones in the blood. The hypothalamus normally controls liver glucose output as well as other metabolic processes in response to the levels of these molecules in circulation. However, when sensing mechanisms become impaired, metabolic abnormalities can occur. Interestingly, there is evidence in mice that high-fat diets blunt the insulin sensitivity of hypothalamic neurons, leading to insulin resistance. Several other speakers talked about glucose sensing in the brain as well, including Dr. Brad Lowell of Harvard Medical School, who discussed how neuronal glucose sensing is necessary for the body to respond to hypoglycemia. Loss of glucose sensitivity in the hypothalamus may contribute to chronic stimulation of the body’s counter-regulatory responses to hypoglycemia, leading to hyperglycemia and type 2 diabetes.
- **Incretins and GLP-1** – Surprisingly, there was only one talk on gut hormones at this conference, but it was certainly worth catching. Dr. Dan Drucker of Toronto University covered three main topics in his fast-paced presentation: the actions of GLP-1 in enhancing b-cell function, the importance of incretins for b-cell function, and the potential for GLP-1 in the preservation of b-cell function in type 1 diabetes. Dr. Drucker explained in some detail that GLP-1’s paradoxical ability to increase insulin output while also preserving b-cells depends on its ability to interact with certain arms of the endoplasmic reticulum (ER) stress pathway to prevent b-cells from undergoing apoptosis, or cell death. He was much more reserved, however, on the possibility that GLP-1 may actually be able to restore lost b-cell mass, and he also discussed the importance of understanding the effects of GLP-1 on the immune system, especially in the setting of type 1 diabetes. We thought this was quite interesting, and it seemed other attendees agreed. One audience member told us, “Well, if Dan Drucker gets up in front of Keystone and says that incretins don’t always restore b-cells, I believe him!” On the flip side, Dr. Drucker also presented some promising ideas regarding the role of GLP-1 in type 1 diabetes and noted that Merck and Novartis are both doing studies of DPP-4 inhibitors in type 1 diabetes.
- **Gene regulation in adipose tissue** – We learned about the important difference between brown fat and white fat from Dr. Bruce Spiegelman of Harvard Medical School. His research has focused on the difference between white adipocytes (bad fat), which store energy and have few mitochondria, and

brown adipocytes (good fat), which dissipate energy and have many mitochondria. The mitochondria in brown adipocytes perform high levels of uncoupled respiration, or the burning of energy to generate body heat. This is why brown fat is linked to increased energy expenditure – obviously a desirable thing in obesity. Dr. Spiegelman and other researchers, such as Dr. Sean Adams of UC Davis, are working to understand the genes that regulate whether adipocytes express brown or white fat-cell genes.

- **Decreasing liver glucose output** – This seems to be a hot area of research. We attended at least half a dozen talks by researchers working on various methods of suppressing hepatic glucose output, which is a big contributor to fasting hyperglycemia in type 2 diabetes. To name just a few: Dr. Barbara Kahn is working on RBP4, a marker of insulin resistance and intra-abdominal obesity, whose over-expression may contribute to hepatic glucose dysregulation in insulin resistance. We also heard Dr. David Moore talk about activation of CAR, a liver nuclear receptor; Dr. Catherine Postic about inhibition of ChREBP, a regulator of fatty acid synthesis; and Dr. Michihiro Matsumoto about inhibition of FoxO1, a transcription factor important in energy sensing – all ways to reduce liver glucose output.

—by Jenny J. Jin

5. Inflammation and Metabolex and J&J's new insulin sensitizer

The idea that inflammation plays a large role in the pathophysiology of diabetes has received interest in recent months, particularly after publication of the DREAM and ADOPT trials. These showed that the thiazolidinediones (TZDs), whose mechanisms of action include reducing inflammation, are effective in both diabetes control and prevention. Below we share our insights on inflammation and diabetes, as well as an intriguing new insulin sensitizer being developed by Metabolex and Johnson & Johnson.

Inflammation and diabetes

Inflammation was a big theme at the Cardiometabolic Health Congress we attended last October in Boston. We heard several talks about the links between obesity, inflammation, diabetes, and cardiovascular disease. The exact mechanisms are unclear, but what is well-established is that increased fat mass, particularly visceral fat, leads to increased secretion of adipokines from adipose tissue, including the inflammatory markers lipoprotein lipase, interleukin-6 (IL-6), C-reactive protein (CRP), tumor necrosis factor alpha (TNF- α), and adiposin. Adipose cells also secrete angiotensinogen, which contributes to hypertension; free fatty acids, which cause dyslipidemia; and plasminogen activator inhibitor-1 (PAI-1), which increases the risk of thrombosis.

One mechanism by which obesity contributes to type 2 diabetes is through the release of hormones and other molecules that cause insulin resistance. Metabolically active fat cells release high levels of resistin, leptin, and lactate, all of which contribute to insulin resistance. They also secrete low levels of adiponectin, a hormone that normally works to prevent metabolic syndrome because it stimulates glucose uptake in skeletal muscle, suppresses liver gluconeogenesis, and increases fatty acid oxidation in the liver and skeletal muscle.

Inflammation is another important mediator in the contribution of obesity to type 2 diabetes. The secretion of inflammatory adipokines from visceral adipose cells attracts macrophages, the large white blood cells that engulf foreign substances and display pieces of those substances on their surfaces as antigens for immune system recognition. These macrophages migrate into the adipose tissue and secrete cytokines of their own – more inflammatory markers that contribute to the chronic inflammation in people with metabolic syndrome and type 2 diabetes. Data on the TZDs to date have suggested that at least part of their glycemia-lowering effect comes from their anti-inflammatory actions, which help reduce insulin resistance and lower blood glucose.

Metabolex and J&J's new insulin sensitizer

We were intrigued, then, to learn more about MBX-102/JNJ-39659100, a new insulin sensitizer being developed by Metabolex and Ortho-McNeil, a subsidiary of Johnson & Johnson. MBX-102 is currently in a 400-patient phase 2/3 study initiated in June 2006, shortly before Metabolex partnered with Ortho-McNeil for the development and commercialization of its metabolic products. Also included in the partnership is MBX-2044, the more potent second-generation version of MBX-102, currently in proof-of-concept phase 2a studies.

We spoke to Metabolex chief medical officer Dr. David Karpf about MBX-102, as well as about Metabolex and J&J's development plans and outlook for the drug. He said MBX-102 is an oral, once-daily partial PPAR- γ agonist/antagonist that has comparable efficacy to TZDs and equal or possibly greater anti-inflammatory effects. The big difference, he said, is that it does not cause the weight gain and edema associated with TZDs. The compound was formerly called metaglidasen, but this name was dropped after Metabolex partnered with Ortho-McNeil – the FDA doesn't allow certain roots in generic names, and "meta" is one of them. There isn't yet a new generic name.

MBX-102's weight neutrality is significant because, as we understand it, the weight gain associated with pioglitazone (Actos, Takeda) and rosiglitazone (Avandia, GSK) actually represents part of the *mechanism of action* of these drugs rather than just a side effect. Dr. Karpf explained that, like these TZDs, MBX-102 is also a strong agonist for the PPAR- γ *trans*-repression pathway, which is responsible for the anti-inflammatory effects and insulin-sensitizing effects of PPAR activation. However, unlike the TZDs, MBX-102 is only a weak agonist or even an antagonist of the PPAR- γ *trans*-activation pathway, which is supposed to be responsible for the adipogenesis and fluid retention that leads to weight gain and edema. Dr. Karpf emphasized that the major problem with TZDs in terms of compliance is the weight gain - which patients dislike - and the major medical problem is edema, which doctors worry about because of the risk of congestive heart failure (CHF). We understand that the edema can be treated with diuretics, but certainly the weight gain is hugely undesirable and there is a huge demand for weight-neutral antihyperglycemics, as evidenced by the strong initial response to Januvia after its October 2006 launch.

Dr. Karpf told us that MBX-102's weight neutrality will allow the drug to more fully realize the role for insulin sensitizers. As a class, sensitizers have the most compelling evidence for slowing down the progression of disease – he characterized them as the ideal oral drugs for type 2 diabetes. The only barrier to use now, he believes, is that the available ones are not safe or tolerable enough to be used to maximum effectiveness or in the early stages of disease, let alone in prevention. He noted that rosiglitazone was never tested in combination with insulin in GlaxoSmithKline's clinical program, even though the combination of insulin and an insulin sensitizer makes a lot of sense. In contrast, Metabolex and J&J are performing their phase 2 studies with patients on insulin – so far, they haven't seen any weight increase versus placebo.

While Dr. Karpf said that for now, Metabolex and J&J will work to get the same label for this drug as currently exists for the TZDs (monotherapy, combination with metformin, sulfonylureas, insulin, or DPP-4 inhibitors), he also talked about the ability of insulin sensitizers to delay diabetes in people with pre-diabetes, referencing TRIPOD, DPP, and DREAM, which all showed 60-70% reductions in diabetes incidence for high-risk individuals on TZDs. For now, he said, sensitizers are clearly the best agents to save islet health and prevent the progression or development of diabetes. In our view, most of the focus right now is on incretins as far as β -cell protection is concerned, but we do agree with Dr. Karpf that existing evidence most strongly backs TZDs. We point out, though, that the TZDs' ability to prevent diabetes development and progression cannot simply be generated to MBX-102 just because it is also an insulin sensitizer. Metabolex and J&J would have to do all the same clinical work that GSK and Takeda have done to convince anyone that they really have a product of comparable efficacy.

The link to inflammation

Metabolex recently presented some new preclinical data at the Keystone symposia showing that MBX-102 reduces inflammation in diabetic mouse and rat models and suppresses the expression of inflammatory genes in both adipose tissue and macrophages. Dr. Karpf explained that the drug has comparable glycemic efficacy and greater anti-inflammatory effects than rosiglitazone in *db/db* mice, as measured by macrophage infiltration into white adipose tissue. MBX-102 also produced comparable or greater decreases in the expression of three key inflammatory genes. We think these data are interesting, but whether the same is true in humans is still unknown. Dr. Karpf did say that anti-inflammatory effect is one of the things they'll be looking at in the phase 3 program. One phase 1 study has shown "substantial reductions" in high sensitivity CRP levels after two weeks of treatment with MBX-102.

As far as the development plan goes, Dr. Karpf noted that PPAR compounds are held to a different set of regulatory guidelines than other compounds. The two-year carcinogenicity studies that the FDA usually requires as part of a phase 3 program in support of a NDA must instead be performed before phase 3 for PPAR compounds. Those studies are ongoing and he anticipates they will be completed in 4Q07, with an end-of-phase 2 meeting planned for 1Q08. We will be eager to see how the potency of this compound emerges. At the conclusion of the end-of-phase 2, J&J will take over the rest of the drug's clinical development and assume all costs for ongoing trials. When we asked about pre-diabetes, he noted that they may pursue a program for that indication as part of phase 4 trials, but they are targeting the diabetes indication for now.

—by Jenny J. Jin

6. Fat Primer: So What is Visceral Fat Anyway?

Chances are, fat people don't particularly care what type of fat they have. What matters to them is how they look in a bathing suit. But all fat is not created equal, and understanding the difference between the various types has important health implications.

There are, in general, two types of fat: visceral fat and subcutaneous fat. Visceral fat is the more serious: it is closely associated with people who are physically inactive and is linked to metabolic syndrome and type 2 diabetes. A closer look at the two types of fat explains why.

Subcutaneous fat is located under the skin and, from a health perspective, is relatively benign. It can be divided into two types.

- **Abdominal** fat: Obese men usually accumulate fat in the subcutaneous abdominal area, producing the characteristic gut associated with male obesity. This is called central, upper body, android, or 'apple-shaped' obesity.
- **Gluteofemoral** fat: Obese woman usually accumulate subcutaneous fat in the gluteofemoral region – around the thighs and butt. This type of obesity is called peripheral, gynoid, or 'pear-shaped' obesity.

The link between gender and regional obesity is not absolute. Many obese men have peripheral fat distribution, and many women have the abdominal variety. In general, subcutaneous fat is not very metabolically active and thus does not contribute to metabolic syndrome, which is why it is called "good" fat. Gluteofemoral fat is less active than abdominal fat, while visceral fat is the most metabolically active.

Visceral or **intra-peritoneal** fat is intra-abdominal and is located inside the peritoneum (the tissue that lines the abdominal wall and covers most of the organs in the abdomen). Visceral fat is directly in contact

with the abdominal organs. Importantly, all visceral fat connects to the circulation via the portal vein (which passes through the liver). Visceral fat is divided into two categories.

- **Omental** fat: A sheet of fat that is covered by the peritoneum. The greater omentum is attached to the bottom edge of the stomach and hangs down in front of the intestines. Its other edge is attached to the transverse colon. The lesser omentum is attached to the top edge of the stomach and extends to the undersurface of the liver.
- **Mesenteric** fat: Fat located in the double layer of the peritoneum (called the mesentery) that connects a part of the small intestine to the back wall of the abdomen. Liu et al (*Diabetes Care*, 2006) have shown that mesenteric fat thickness is an independent determinant of metabolic syndrome and is associated with carotid intima-media thickness (CIMT), a measure of atherosclerosis.

Why visceral fat is bad

The lipolytic hormones (i.e. catecholamines) are most active in the visceral fat. The anti-lipolytic hormones (i.e. insulin, prostaglandins, and adenosine) are most active in the subcutaneous fat. This means lipids/free fatty acids are always more rapidly mobilized from visceral than subcutaneous fat. A common theory is that visceral obesity leads to faster mobilization of fatty acids to the portal system, both because lipolysis from visceral cells is relatively fast and because there is more fat in the visceral depot. The resulting high levels of ‘portal’ free fatty acids can impair liver function, causing glucose intolerance, dyslipidemia, and hyperinsulinemia.

In a July 2004 *Nutrition Reviews* paper, Dr. F Xavier Pi-Sunyer wrote: “Both cross-sectional and longitudinal studies have related central fat to type 2 diabetes mellitus and cardiovascular disease, independent of BMI. The mechanism may relate to increased lipolysis causing the liver to increase glucose and v-LDL output, while muscle uses less. This leads to a rise in blood glucose and triglycerides, a drop in HDL cholesterol, and an increase in small, dense LDL particles. There is also an increase in blood pressure and inflammatory markers. Certain populations put on excess fat more centrally than others. These include Asian populations.” We think this is an excellent summary of the knowledge to date – we have a general idea that metabolically more active visceral fat causes damage, but there seem to be so many mechanisms that it is difficult to study this topic in a straightforward way. Dr. Pi-Sunyer’s comment in genetic differences in the predisposition for putting on visceral fat is also a very relevant one going forward as obesity and diabetes become a rising problem in all developing countries, and especially in Asia.

Notes on usage and wording

Many doctors will say “abdominal fat” when they’re actually talking about “visceral fat,” because central or abdominal adiposity (fattiness), is often - though not always - associated with visceral adiposity. Doctors will also use “peripheral fat” interchangeably with “subcutaneous fat,” probably because subcutaneous fat is not very metabolically active. Technically, the only way to really measure the amount of visceral versus subcutaneous fat a person has in their abdominal region is to perform a CT or MRI scan. Since this is not practical as a general diagnostic tool, most doctors simply measure waist circumference as a proxy for visceral fat. Current guidelines suggest that a waist circumference greater than 40 inches in men or 35 inches in women is cause for worry.

Even more fat

Finally, there are three other types of fat, rarely mentioned but worth noting.

- **Retroperitoneal** fat is located behind the abdominal cavity. Retroperitoneal fat is intra-abdominal, so it must be drained through the portal vein and is probably just as bad as visceral fat. However, it isn’t discussed much because people tend not to have very much of it.
- **Perirenal** fat describes the layer of fat surrounding the kidney. Thick perirenal fat is associated with lipodystrophy (dysregulation of fat metabolism).

- **Orbital** fat is located under, over, and behind the eyeball to protect and cushion the eye. As far as we know, this has nothing to do with metabolic syndrome.

—by Jenny J. Jin

7. SGLT2 Inhibitors: An Emerging Class in Type 2 Diabetes and Obesity

The sodium glucose co-transporter 2 (SGLT2) inhibitors are a relatively new class of molecules in development for type 2 diabetes and obesity. SGLT2 is a sodium/glucose pump found in the kidney. As you know, the role of the kidney is to filter waste molecules out of the bloodstream. When blood enters the nephron (the basic operational unit of the kidney), it gets squeezed through what can be thought of as a coarse-grained filter. Proteins and larger objects including blood cells are excluded but anything smaller (including glucose) passes through the filter and into a chamber called the glomerulus as filtrate. From that point on, the job of the nephron is to pump everything useful that passed into the filtrate back into the bloodstream before the filtrate goes to the bladder as urine. SGLT2's job is to pump glucose out of the filtrate. It must do this against the concentration gradient of glucose, which is an energetically unfavorable process. This is why SGLT2 couples the transport of glucose to the transport of sodium, which is energetically favorable.

SGLT2 belongs to a family of eleven sodium substrate co-transporters. SGLT2 is the main transporter of glucose in the kidney, but SGLT1, a sodium glucose/galactose transporter, is also found in the kidney. SGLT1 is mainly expressed in the small intestine but has also been found in human heart cells as well as in rat and pig cerebral blood vessels, where it may transport glucose past the blood-brain barrier. Thus, inhibition of SGLT1 is more pharmacologically risky than SGLT2, especially since SGLT1 is a low volume transporter and probably does not account for very much kidney glucose reabsorption. SGLT3 is a glucose-sensing sodium channel found in the small intestine and thought to play a role in nutrient sensing and intestinal motility. SGLT4 is a glucose/mannose/fructose pump found in the small intestine and kidney. The other known members of the *SLC5* gene family are not involved in glucose transport.

SGLT2 inhibitors prevent glucose from being pumped out of the glomerular filtrate, thus causing glucose to be lost into the urine. The first SGLT2 inhibitor was phlorizin, a natural product from fruit tree bark first discovered in 1835 to cause 'phlorizin diabetes' or glycosuria (sugar in the urine) when taken in high doses. The chemical structure of phlorizin includes a glycoside, or a sugar molecule, which mimics the structure of glucose and allows phlorizin to bind competitively to the SGLT2 pump and prevent it from pumping glucose. Unfortunately, phlorizin is not very orally available because it is degraded in the digestive tract, excluding it from being a good drug candidate.

Japanese companies pioneered the discovery of the newer SGLT2 inhibitor molecules and hold most of the existing patents on this chemical space. All small-molecule SGLT2 inhibitors are analogs of phlorizin and like phlorizin include glycoside moieties. **Tanabe Seiyaku** Co. discovered the first orally available phlorizin analog, T-1095, which was patented in 1998 but currently does not appear in the company's listed clinical pipeline. Other companies that have patented phlorizin analogs include **Kissei Pharmaceutical Co.** beginning in 2001, **Bristol Myers-Squibb** (2001), **Kotobuki Pharmaceutical** (2001), **Ajinomoto Co.** (2002), **Kyowa Hakko Kogyo Co.** (2003), **Fujisawa** (2004), **Yamanouchi Pharmaceutical** (2004), **Taisho Pharmaceutical** (2004), **Aventis Pharma** (2004), **Boehringer Ingelheim International GmbH** (2005), and **Janssen Pharmaceutical** (2005). Preclinical studies by various companies have shown that SGLT2 inhibition restores normoglycemia in animal models of diabetes, with accompanying improvements in β -cell function, insulin resistance, and lipid profiles – we assume that these are indirect effects of treating hyperglycemia.*

* Handlon AL. "Sodium glucose co-transporter 2 (SGLT2) inhibitors as potential antidiabetic agents." *Expert Opin Ther Patents*. 2005. 15(11):1531-1540.

The following companies have SGLT2 inhibitors in clinical development

- **Bristol Myers-Squibb** entered a collaboration agreement with AstraZeneca on Jan 11 for the development and commercialization of dapagliflozin (BMS-512148), currently in phase 2b trials for type 2 diabetes. The collaboration applies worldwide, excluding Japan.
- **GlaxoSmithKline/Kissei**'s two lead SGLT2 inhibitors were both in phase 2 development as of February 2006. GSK-189075 was in development for type 2 diabetes and GSK-869682 was in development for obesity. We note that in October 2002 GSK in-licensed Kissei's SGLT2 inhibitors, receiving exclusive rights to develop and market the compounds worldwide, excluding Japan, Korea, China and Taiwan.
- **Sanofi-Aventis**'s SGLT-2 inhibitor AVE2268 is in phase 2a studies for type 2 diabetes. The company is also doing preclinical work on a SAR7226, a SGLT1/SGLT2 inhibitor for type 2 diabetes.

A few companies are working on other approaches to SGLT2 inhibition. **Theratechnologies** presented pre-clinical data at ENDO 2005 on two peptide antagonists of SGLT2. **ISIS Pharmaceuticals** is doing preclinical work on antisense inhibitors of SGLT2 production – the idea here is to administer nucleic acids that are complementary to the messenger RNA (mRNA) of the SGLT2 protein. This causes the body to degrade the target mRNA before it can code for the production of the protein, thus preventing SGLT2 from being made.

We think one of the attractive features of the SGLT2 inhibitor class is its potential both in normalizing hyperglycemia in patients with type 2 diabetes and in helping eliminate excess calories in obese patients – two patient populations that often overlap. The kidney reabsorbs about ~180 g of glucose per day, with each gram equal to ~4 Kcal. SGLT2 accounts for most of this reabsorption, which means complete SGLT2 inhibition could allow patients to excrete hundreds of Kcal per day. Diabetes patients could potentially normalize their glucose with less insulin, while also (perhaps) losing weight – a prospect we find extremely exciting.

Some caveats: SGLT2 inhibition would almost certainly lead to polyuria, or increased urine volume. This side effect is more inconvenient than harmful, but we imagine it's not one that patients would like very much. On the other hand, if SGLT2 inhibitors cause weight loss, we think people would be willing to schedule a few extra bathroom breaks to take the drugs. More serious potential side effects include kidney and urinary tract complications. Diabetes patients tend to have higher rates of urinary tract infections, though some studies have shown that this is not linked to glycosuria. We are also curious about whether the presence of glucose in the distal sections of the nephron, where glucose is normally not present, would contribute to renal glucotoxicity. As we understand it, hyperglycemia in the glomerulus and proximal sections of the nephron is the main issue in diabetic nephropathy, and SGLT2 inhibitors would actually help prevent hyperglycemia.

When we first heard about the mechanism of SGLT2 inhibitors, we immediately wondered whether they would cause hypoglycemia, especially during fasting. However, this does not appear to be a problem. The most promising evidence so far in favor of SGLT2 inhibitors is the existence of people with genetic SGLT2 defects, reported by Santer et al in *J Am Soc Nephrol* (2003). The fourteen individuals they studied with double mutations had higher water intake and urine volume than typical but were not hypoglycemic or have any renal disease associated with the mutations. We imagine that perhaps the lack of hypoglycemia is due in part to the presence of homeostatic mechanisms for increasing liver glucose output in response to low blood glucose. These counter-regulatory mechanisms are often lost in intensively managed type 1 diabetes patients, which may mean that SGLT2 inhibitors are not good drug candidates for type 1 patients or type 2 patients with impaired hypoglycemic response. The fact that there is an upper limit to the amount of glucose that can be eliminated through SGLT2 inhibition probably

helps prevent hypoglycemia, but we imagine it also means that SGLT2 inhibition would not be sufficient to restore normoglycemia in patients with higher blood glucose levels and A1c.

—by Jenny J. Jin

8. In the News

A new addition to DCU, this column will highlight interesting or important events in recent diabetes news that do not appear as full stories or in the company watch. In this issue, read about a new islet farm, the discoverer of leptin, and a recent podcast on the CHICAGO trial.

- **Prestigious Kovalenko Medal awarded to discoverer of leptin:** Dr. Jeffrey Friedman of Rockefeller University will receive the National Academy of Science's Kovalenko Medal at its April 29 meeting in Washington. Friedman discovered leptin, and his work opened the door to understanding the physiologic system of body weight and the pathophysiology of obesity. The medal, plus \$25,000, is awarded every three years for contributions in the medical sciences. Friedman is head of the Molecular Genetics lab at Rockefeller and a Howard Hughes Medical Institute investigator.
- **Dave.md podcast raising doubts about CHICAGO trial:** On Jan 15, powerhouse editor-in-chief of dave.md, Dr. Steven Marso, discussed the clinical and scientific implications of the CHICAGO trial on his regular audio podcast called "This Month in Diabetes." The CHICAGO trial, by Mazzone et al, showed that pioglitazone slows increases in carotid intima-media thickness (CIMT), a surrogate predictor of cardiovascular events, compared to glimepiride. Dr. Darren McGuire of the University of Texas and Dr. Nikolaus Marx of the University of Ulm in Germany joined Dr. Marso on the podcast. The discussion made clear that it is difficult to establish what the CHICAGO results may actually contribute to clinical practice. Questions left unanswered in the trial and paper were whether pioglitazone improved CIMT independently of improvements in glycemic control and how CIMT actually correlates with cardiovascular risk. Though the paper's authors point out that differences in A1c between the two groups manifested later than CIMT differences, Dr. Marx still thought the effects on CIMT could be due at least partially to metabolic improvements undetected by the study's methods. Another doubt is whether reducing CIMT will actually reduce cardiovascular risk, as no studies currently suggest that it will. Nevertheless, after ADOPT and DREAM, CHICAGO certainly doesn't hurt the profile of TZDs.
- **New facility to produce porcine islets for transplants:** A facility in Wisconsin that will produce a steady supply of biosecure porcine islets to implant in diabetic patients will be operating by the end of February. A Washington-based non-profit dedicated to finding a cure, the Diabetes Research & Wellness Foundation (DRWF) has provided \$6.2 million for the 21,000 square-foot facility, which will house pigs in a contamination-free environment. The project is called the Spring Point Project, led by president Tom Cartier and inspired by a famous diabetes researcher on the team, Dr. Bernhard Hering from the University of Minnesota. His March 2006 *Nature Medicine* article showed diabetic monkeys cured with porcine islet transplants. The co-author of this paper, Henk-Jan Schuurmann, is the project's CEO. Its goal is to conduct human trials within three years and to receive FDA approval for porcine islet transplants in humans soon after. A geneticist is on staff to breed the pigs for high-islet production, and a South Dakota farming community is volunteering to oversee their care. www.springpointproject.org
- **AstraZeneca, Healthy Choice, Subway promote workplace wellness:** The three companies announced Jan 8 that they will help sponsor the American Heart Association (AHA) workplace wellness program, called Start!, which seeks to promote physical activity and other healthy habits

in the workplace. We think it's appropriate that a major pharmaceutical company is getting behind the movement to promote workplace wellness, which we think is one of the best places to initiate programs for preventing metabolic syndrome and diabetes.

—by Daniel A. Belkin

9. Reviewing the Diabetes Literature: American College of Physicians weighs in on type 2 diabetes

Below is our list of the 25 most important articles on diabetes and obesity published since our last DCU, along with some main takeaways from the review we wrote on our favorite paper of the month. Our team is always looking for the most relevant articles on new diabetes research, and this month we've compiled papers from journals including *Annals of Internal Medicine*, *Diabetes Care*, *Diabetes*, *JAMA*, *Nature*, *NEJM* and more.

- *Am J Clin Nutr - FABP2 Ala54Thr genotype is associated with glucoregulatory function and lipid oxidation - Weiss et al:* The fatty acid binding protein 2 (FABP2) gene regulates the uptake and metabolism of long-chain fatty acids from food and plays a role in lipid oxidation. Roughly half of the 122 adults in this study had an Ala54Thr mutation in this gene; these people oxidized lipids at a higher rate and had lower glucose tolerance and insulin action, possibly predisposing them to a higher risk of diabetes. We thought this was an interesting new finding in the search for genetic markers of diabetes.
- *Arch Int Med - The effect of weight loss on C-reactive protein - Selvin, Paynter, Erlinger:* Weight loss decreases levels of CRP, a marker of inflammation. The conclusion – that weight loss reduces inflammation – is not surprising, but an important implication is that if some of the complications of obesity such as CVD and diabetes are mediated through inflammation, then anti-inflammatories may be one way to treat the complications of obesity without actually losing weight.
- *Arch Ped Adol Med - Resource utilization and expenditures for overweight and obese children - Hampl et al:* Of the children aged 5-18 yrs included in this study, 18% were overweight and an incredible 22% were obese. Older (>10 yrs), female, and Medicaid children were more likely to be obese. Surprisingly, only 43% of the obese children had been “diagnosed” with obesity. Both diagnosed and undiagnosed obese children had more lab tests performed than children of normal weight. The mean difference in health care cost between diagnosed obese children and normal-weight children was \$172 annually – clearly a number that goes up sharply over time.
- **** Clin Chem - CRP and oxidative stress markers among persons 10-18 years old - Kelishadi et al:* Inflammation and oxidative stress are correlated in healthy non-diabetic children. Both correlate with abdominal obesity, but not with BMI or subcutaneous fat, so we know the type of fat matters in kids. Would waist circumference be a more useful cardiometabolic measure than BMI? The presence of oxidative stress in non-diabetic children suggests that oxidative stress may have a role in promoting CVD independently of hyperglycemia. We don't yet know the cause-effect relationship between inflammation and oxidative stress or how much each contributes independently to CVD risk. To puzzle this out would require a longitudinal study – very difficult to do.
- **** Diabetes Care - The accuracy of the FreeStyle Navigator continuous glucose monitoring system in children with type 1 diabetes – Wilson, Weinzimer et al (The DirecNet Study Group):* In this study, the Navigator's median relative absolute difference (RAD) was 12% inpatient and 14% outpatient, very impressive accuracy. Accuracy did not vary with day of sensor use and was better at night than during the day, though actual performance was poorer during the day because of larger and more frequent glucose excursions. Despite the Navigator's relatively good performance, its accuracy and precision were still not where they would need to be for a replacement indication to BGM; we don't believe a replacement indication should be necessary for reimbursement but it has been difficult to

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

assess what the payors hope to see. Overall, we see this as a quite positive paper, since DirecNet papers are typically quite tough reading.

- *** *Diabetes Care - Primary prevention of cardiovascular diseases in people with diabetes – ADA/AHA*: This consensus statement nicely harmonizes the two organizations' recommendations for preventing CVD in diabetes patients. There are clear guidelines on weight reduction, physical activity, control of blood pressure, lipid management, smoking and aspirin. This piece reflects the fact that CVD and diabetes are very closely intertwined, and we hope it indicates the two sides are trying to cooperate instead of hurling spears at each other.
- *** *Diabetes Care - The NECP-ATP III, IDF, and WHO definitions of the metabolic syndrome as predictors of cardiovascular disease and diabetes - Lorenzo et al*: The three definitions assessed in this study identified CVD and diabetes risks with similar accuracy. The metabolic syndrome is a useful predictor of diabetes independent of its association with glucose intolerance. We consider this another piece of evidence in favor of the clinical use of metabolic syndrome as a diagnostic tool.
- *Diabetes Care - Adiposity compared with physical inactivity and risk of type 2 diabetes in women - Rana et al*: Obesity and physical inactivity both contribute independently to type 2 diabetes. This study suggests obesity contributes much more. Compared to physically active lean women, the relative risk of diabetes was 16.75 for obese inactive women, 10.74 for obese active women, and 2.08 for lean inactive women. Thus, while physical activity certainly confers benefits for obese patients, losing weight would help more... alas, an efficacious way to do this is currently lacking.
- *Diabetes Care - Achieving glycemic goals in type 2 diabetes - Bloomgarden*: This is the fourth in a brilliant series of continuing articles reporting presentations from the 2006 ADA meeting. This one discusses the importance of achieving glycemic goals, with a particular focus on insulin treatment, as well as some new potential treatments such as cytokine modulation. Also included are talks on insulin sensitizers – in particular, PROactive and TZDs in nonalcoholic steatohepatitis.
- *Diabetes, Obesity, & Metabolism - Thiazolidinedione insulin sensitizers and the heart: a tale of two organs? - Buckingham, Hanna*: This review looks at the benefit-risk profile of TZDs with respect to the heart, discussing in detail the causes of heart failure in TZD patients. After comparing the risk of heart failure to that of cardiovascular disease, the authors conclude that the benefits outweigh the risks and TZDs should be used early in type 2 diabetes. This may be statistically true, but edema is highly undesirable in already obese patients. Weight-neutral insulin sensitizers could be ideal, we think.
- *** *Diabetes - Liraglutide reduces body weight and food intake in obese candy-fed rats whereas vildagliptin does not - Raun et al*: Liraglutide reversed diet-induced obesity in non-diabetic rats by reducing caloric intake, improving food preferences, and increasing metabolic rate. We thought the choice of vildagliptin as a comparator was odd because it is known to be weight-neutral, but the authors say they wanted to compare the mechanisms of GLP-1 analogs and DPP-4 inhibitors. Both drugs reduced β -cell mass even though vildagliptin rats did not lose weight - one hypothesis is that liraglutide's effects on insulin sensitivity or β -cell function depend more on weight loss than vildagliptin's.
- *** *Diabetic Medicine - Diabetes risk in British adults in mid life- a national prevalence study of glycated haemoglobin - Thomas et al*: The authors measured A1c values from 7,799 non-diabetic individuals born in 1958 in England, Scotland, and Wales. The majority (54.8%) had A1c's between 5.0% and 5.4%, a result that did not vary significantly by sex, socioeconomic status, or area of residence. However, above and below this range, being female, having low socioeconomic status, and having a high BMI contributed to higher A1c's. This is useful information, but we wish other factors had been considered as well, such as ethnicity, family history of diabetes, etc. Perhaps in future studies...
- *Diabetic Medicine - Association of diabetes-related emotional distress with treatment in primary care type 2 patients - Delahanty et al*: Patients on insulin report higher diabetes-related emotional distress compared to those on diet and exercise or oral medications. The authors note that greater disease severity and burden of self-care may explain this, but we would think there is probably also a

psychological contribution; patients usually think they are sicker if their doctors put them on insulin. We doubt the same worries would be linked to initiation of Byetta, though.

- *Diabetic Medicine - Pancreatic β -cell function is altered by oxidative stress induced by acute hyperglycaemia - Miyazaki et al:* The authors measured two markers of oxidation state during a 75-g oral glucose tolerance test in patients with normal and impaired glucose tolerance as well as patients with diabetes. Higher oxidative stress was associated with diminishing β -cell function. This study reminds us of the importance of glycemic variability, though we note that because it was an observational study, it only shows a link between oxidative stress and impaired β -cell function, not a causal relationship.
- **** Diabetologia - The effects of acute hypoglycaemia on memory acquisition and recall and prospective memory in type 1 diabetes - Warren et al:* The formation and recall of memories of words and stories are impaired during hypoglycemia. Patients with impaired hypoglycemia awareness experience a smaller but still significant decline compared to patients with normal awareness, perhaps because their brains are partially adapted to functioning during hypoglycemia. We think this provides more evidence for controlling glycemic variability, in order to prevent hypoglycemia-related memory problems.
- **** Diabetologia - Progression from IFG and IGT to diabetes in a high-risk screening programme in general practice - Rasmussen et al:* The ADDITION study identified adults with diabetes, IGT, and IFG in a Danish high-risk primary care population and found the one year incidence of diabetes to be 17.6% in people with IFG and 18.8% in people with IGT. This is higher than previously reported in population-based observation studies. The study had several flaws that may have biased its numbers, but we do think it provides further support for aggressive interventions in pre-diabetes.
- *Diabetologia - A comparison of twice-daily exenatide and biphasic insulin aspart - Nauck et al:* Compared to twice daily 30/70 NovoMix injections, twice daily exenatide injections provided similar A1c control and better postprandial control. Exenatide caused more GI problems but also caused weight loss while biphasic aspart caused weight gain. This study was first presented at EASD in 2006, but the paper is worth noting – Dr. Nauck is a powerhouse as many readers know.
- *Intl J Obesity - Clinical significance of adaptive thermogenesis - Major et al:* This review paper, along with an accompanying editorial by Dulloo, discusses one of the major reasons why people have trouble maintaining weight loss – there is a large decrease in energy expenditure in people who lose weight so that they actually use less energy than would be expected for their new body weight. This has traditionally been thought to be a genetic response, but the authors suggest that environmental factors play a role as well. Very intriguing, we think.
- *Intl J Obesity - Adiponectin, insulin resistance, and metabolic syndrome in type 2 diabetes - Mojiminiyi:* With all the interest lately in adiponectin, we wanted to point out this study, which found that adiponectin levels are inversely correlated with age, obesity, insulin resistance, and high sensitivity-CRP. We understand that there's actually a link between the TZDs' effects on increasing both adiponectin and subcutaneous fat, so increasing adiponectin is probably not a useful treatment target, but the hormone does seem to play an important role in metabolic regulation.
- *Intl J Obesity - The association between early childhood stunting and weight status in late adolescence - Walker, Chang, Powell:* In this prospective cohort study, children with stunted growth at 2 years remained shorter and had lower BMIs at age 17-18 years than children with normal growth at 2 years. The authors say this goes against the current thinking that low intra-uterine growth and birth-weight are associated with catch-up growth and later obesity, but perhaps the discrepancy arises because size at birth and at 2 years are not well-linked. The lesson, we think, is that small toddlers (but perhaps not small babies) will stay small as teenagers. A good argument against overfeeding the baby.
- **** JAMA - Law as a tool to facilitate healthier lifestyles and prevent obesity - Gostin:* Gostin suggests eight areas where the law can be used to prevent obesity: food content disclosure, tort liability for food makers, surveillance of obesity, regulation of food marketing to children, taxation of unhealthy foods, school and workplace policies, improving the environment for healthy living, and banning

- harmful foods. He believes the supposedly individual decisions that lead to obesity are actually socially embedded, which is why public policy changes are needed to combat obesity. We agree.
- *Lancet - Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis - Elliott, Meyer*: The association of antihypertensive drugs with incident diabetes is lowest for angiotensin-receptor blockers (odds ratios 0.57 compared to diuretics) and angiotensin converting-enzyme inhibitors (0.67) followed by calcium channel blockers (0.75), placebo (0.77), β -blockers (0.90), and diuretics. This suggests to us that use of β -blockers and especially diuretics should be avoided, since alternatives are available.
 - ^{***} *Nature - An obesity-associated gut microbiome with increased capacity for energy harvest - Turnbaugh et al*: There is a two-way relationship between gut bacteria and body weight. The proportion of Firmicutes and Bacteroidetes bacteria in the gut differs between lean and obese individuals. The gut microbiota of obese *ob/ob* mice are more efficient at calorie extraction than those of lean mice, and cause more weight gain when transplanted into germ free mice. The gut microbiota of obese humans who lose weight becomes more like that of lean humans. This story was reported in the Jan 24 issue of *JAMA* and widely circulated in the popular press. However, we agree with an accompanying *Nature* editorial by Bajzer and Seeley that cautions more research is needed before jumping to conclusions.
 - ^{***} *NEJM - Obesity and diabetes in the developing world - A growing challenge - Hossain et al*: This article provides a sobering assessment of the growth of obesity, diabetes, and their morbidities in the developing world. Obesity leads to type 2 diabetes, cardiovascular disease, and some cancers at higher rates in developing countries than in the developed world. Microvascular disease – the authors focus on diabetic nephropathy – is a huge and growing burden and can represent a death sentence to people who cannot afford treatment. We heard a lot about this at IDF, and it is promising that the issue is gathering attention in prestigious journals such as the *NEJM*.
 - ^{***} *NEJM - Public reporting and pay for performance in hospital quality improvement - Lindenauer et al*: This 2-year study examined the effect of financial incentives on quality improvements in 613 hospitals. While pay-for-performance hospitals showed greater improvements than control hospitals, when adjusted for baseline differences the improvements were only 2.6-4.1% better. We believe pay-for-performance has its merits and that financial incentives have the power to stimulate a desired behavior. That said, we also believe that the complexity and cost of implementation should be weighed against the seemingly limited benefits shown in this study.

Below we present our main takeaways from a full review we wrote on the *Annals of Internal Medicine* “In the Clinic” feature on type 2 diabetes. If you would like a copy of the full review, please write us at litreviews@closeconcerns.com. *American College of Physicians. “In the Clinic: Type 2 Diabetes.” Annals of Internal Medicine 2 Jan 2007, 146(2), ITC:1-16.*

Main takeaways: 1) **The *Annals of Internal Medicine* has a new monthly section called “In the Clinic” that gives PCPs useful guidelines on common conditions.** The first issue is on type 2 diabetes, and it’s fairly comprehensive, striving to include diagnosis, screening, prevention, evaluation, treatment, and how to improve clinical practice. 2) **The recommendations in this guide are significant because they will reach many primary care physicians** – the journal has a circulation of about 85,000 physicians and other healthcare providers. The American College of Physicians (ACP) funded this report. 3) **The pharmacotherapy options given are very up-to-date.** We were particularly impressed with the detailed sections on exenatide (Byetta) and pramlintide (Symlin). Sitagliptin (Januvia) also receives mention, as does inhaled insulin. Insulin glulisine (Apidra) is mentioned but not insulin levemir (Detemir), which surprised us since long acting analogs are often the first insulin treatment for type 2 patients. Overall, incretins receive the limelight treatment while inhaled insulin gets a much colder tone, which is consistent with the many physician and nurse discussions we have had over the last year. 4) **The screening and therapy recommendations are more conservative.** Despite the negative durability and side effect conclusions from the ADOPT data, sulfonylureas and metformin remain the suggested first-

line therapies. The guide discourages more than twice-daily insulin dosing, which we found surprising, though given the audience, we assume that more frequent dosing would be considered too complex. The guidelines only advocate type 2 screening for middle-aged adults with risk factors. **5) The recommendations on home glucose monitoring are progressive.** The guide advocates home monitoring for patients on oral medications and insulin alike and alludes to the possible role of postprandial glucose in outcomes. **6) Prevention gets a positive look.** The guide gives as much attention to pharmacotherapy as it does to diet and exercise and advises doctors to “consider” all the options for patients with pre-diabetes: metformin, acarbose (Precose), and rosiglitazone (Avandia).

—by Jenny J. Jin

10. Upcoming Conference Preview

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

<http://www.motilitysociety.org/>

Spend an excellent weekend in the Bahamas at this year’s American Motility Society (AMS) meeting on “Diabetes and the Gut,” which is a fitting topic considering the explosion of incretin therapies in the past year. We can’t wait for this meeting, though note the concentration on basic science will be very heavy so not for the faint of heart. Below we highlight a few talks of interest.

On Thursday evening, from 6:00- 6:45 p.m., incretin luminary Dr. Bo Ahren of Lund University in Sweden will discuss “*Metabolic and Endocrine Effects of GI Hormones in Diabetes.*” Afterwards, at 7:00- 7:45 p.m., we’ll learn more about the mechanisms of inflammation in “*Diabetic Alterations in Inflammatory Pathways,*” by Dr. Steven Shoelson of Harvard Medical School and the Joslin Diabetes Center. In light of Dr. Irl Hirsch’s comments in his interview this issue, we think this will be especially informative.

On Friday from 11:30 a.m.- 12:15 p.m., Dr. Anthony Ferrante from Columbia will deliver a talk on how “*Obesity Modulates the Expression of Neuropeptides and Hormones.*” Neuropeptides are very of the moment due to Amylin’s work – this should be fascinating.

On Saturday morning at 8:00- 8:30 a.m., Dr. Giamila Fantuzzi of the University of Illinois will discuss “*Adiponectin/ Leptin/ Grhelin and Intestinal Inflammation.*” We certainly won’t want to miss the abstract presentation directly after, from 8:30- 8:45 a.m. on the “*Effect of DPP-4 inhibitor, vildagliptin, on gastrointestinal function, nutrient intake and glucose metabolism in type 2 diabetes.*” The paper is by A Vella et al of the Mayo Clinic.

On Sunday morning, from 8:00- 9:00 a.m., is a talk we’ve personally been looking forward to: “*Type 1 Diabetes Therapy: Beyond Islet Cell Replacement,*” by Dr. Massimo Trucco of the University of Pittsburgh – we’re always interested to see the latest thoughts on this subject as we are skeptical ourselves. Then, from 9:15- 10:00 a.m., is a talk on “*Peripheral Glucose Sensing by the Nodose Ganglion*” by Dr. Chung Owyang from the University of Michigan. Out there? Well, we always like to keep you updated on glucose sensing. See you on the beach...

- **AACE, April 1-15, Seattle, WA, <http://www.aace.com>**

Once again, this year’s AACE offers a packed and exciting program – and can we tell you how excited we are it is in Seattle! A number of interesting satellite symposia will take place on Wednesday, April 11, and then AACE is kicks off Thursday morning for sessions and symposia over the next four days. Thursday and Saturday consist of general sessions in the morning and concurrent workshops in the afternoon. Friday and Sunday consist only of general sessions.

The keynote speech on Friday morning is intriguing. The title is “*Microsoft and Healthcare*” and it will be presented by Microsoft’s Corporate Vice President for Health Strategy Peter Neupert –

fascinating that the speaker is from Microsoft. To bring us up to speed at the start of the conference (from 9 a.m. to 9:45 a.m.), Dr. Irl Hirsch, of the University of Washington, will identify new and proven strategies for treating both type 1 and 2 in “*What Has the Last Year Taught Us?*” This promises to be one of the best talks of the year you’ll hear.

What follows is a preview of the talks that most interest us.

Pediatric type 2: Given the huge increase in obesity and type 2 diabetes in children and adolescents, we highlight a Thursday workshop on “*Insulin Resistance Disorders in Pediatrics*” from 2:00-3:15 p.m., led by Dr. Phil Zeitler of the Barbara Davis Center for Childhood Diabetes. Then Saturday features a general session from 11:15 am- noon called “*Type 2 Diabetes in Adolescence and its Consequences.*” The talk will be given by Dr. Peter Bennett, Scientist Emeritus of National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

General type 2 care: On Wednesday, Amylin supports a symposium called “*Designing an Architecture for Change: Constructing Optimum Treatment Regimens for Type 2 Patients,*” from 3:00– 4:30 p.m. On Thursday from 8:15 a.m. - 9:00 a.m., Dr. Steven Kahn will discuss “*The Beta Cell: Bench to Bedside.*” He is from the University of Washington and is an incredibly impressive speaker – we hung on his every word at EASD and IDF last year. His talk focuses on how the latest basic and clinical research contributes to what we know about β -cells in type 2.

Invasive treatments: To start a Thursday session on “*Bariatric Surgery,*” from 10:30 a.m.- noon, will be Dr. David Cummings from the University of Washington talking about “*The Science Behind the Surgery.*” On Friday from 10:30 a.m.- 11:15 a.m., Dr. Paul Robertson of the University of Washington will discuss “*Islet Transplantation: Where Are We Now?*” We are eager to hear this session, since there has not been broad discussion in the area in recent years.

Drugs – insulin and incretins: On Wednesday, there are two relevant satellite symposia. Merck is sponsoring one on “*New Strategies for Achieving Glycemic Control: The Role of Incretin Hormones*” from 1:00 p.m. - 2:30 p.m. Then, from 3:00 p.m.- 4:30 p.m. will be an Amylin-supported symposium called “*Man Cannot Live on Insulin Alone: Augmenting Therapy for Better Outcomes.*” On Friday, supported by Sanofi, a breakfast symposium on “*Physiologic Insulin Regimens in the Management of Hyperglycemia in Chronic and Acute Settings*” takes place at 6:15 a.m. - 7:45 a.m. Or, at the same time, choose the Novartis-sponsored symposium on “*The Role of Incretin Therapies in Long-term Glycemic Control: What’s the Next Move?*” There will be lots of us there if you miss anything...

Complications: On Thursday, Dr. Alan Chait and Dr. John Brunzell from the University of Washington will give a talk from 2:00 p.m. - 3:15 p.m. on “*Cardiovascular Disease and Diabetes,*” in which they will discuss the CV risks associated with diabetes, how to treat them, and what benefits may be expected from treatment. A workshop on “*Diabetic Neuropathies: The Need to Test for Automatic Neuropathies and Practical Technologies for Doing So*” occurs Saturday from 2:00 p.m. - 2:50 p.m. and is led by neuropathy expert Dr. Aaron Vinik from Eastern Virginia Medical School.

Prevention: On Wednesday at 7:15 p.m. - 8:45 p.m., Takeda hosts a symposium called “*Realizing a Butterfly Effect: Predicting and Preventing Type 2 Diabetes and Related Vascular Disorders.*” On Wednesday at 3:00 p.m. - 4:30 p.m., there will be a symposium supported by Sanofi called “*Why Weigh? A Mandate for Early Intensive Treatment of Abdominal Obesity and Cardiometabolic Risk.*” We think this will likely talk about delaying progression to type 2. Then, a GSK-supported breakfast symposium on Thursday from 6:15 a.m. - 7:45 a.m. will be on “*Implementing New Data to Treat the Patient at Risk for Type 2 Diabetes.*”

Critical care: On Wednesday there will be a symposium called “*A New Focus on Inpatient Diabetes: The Vital Role of the Endocrinologist,*” supported by an educational grant from Novo Nordisk, from 5:00 p.m. - 6:30 p.m. At the same time is a Lilly-supported symposium on “*Current Strategies and Needs for Managing the Critically Ill Patient with Diabetes.*”

Continuous glucose monitoring: On Friday from 1:00 p.m. - 2:30 p.m. is a symposium supported by Medtronic on “*Optimizing Diabetes Outcomes with Real-Time Continuous Glucose Monitoring.*” We’ll hope to hear a bit more about the STAR trials here. On Saturday Dr. Irl Hirsch will lead a workshop on “*Novel Approaches in Therapy for Diabetes.*” From 2:00 p.m. - 2:50 p.m., he will discuss CGM and how potentially to use downloaded data as well discuss his views on exenatide).

—by Daniel A. Belkin and Kelly L. Close

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