

Diabetes Close Up April 2007, No. 68 Early Warning: The Spotlight on Pre-Diabetes

#### TheShorterVersion

From the Editor:

What a spectacular weekend! Half our company attended the Hope Gala, a JDRF Bay Area fundraiser, on Saturday night. Securities industry powerhouse Phil Stapleton of Conifer Securities was the honoree – winner of the Living and Giving Award – and he gave a moving speech about his exposure to diabetes over time. It was amazing to see all these impressive people united by the goal of improving diabetes care or eliminating the disease entirely. Bighearted sponsors included Abbott, LifeScan, Warburg Pincus and many, many others. \$1.1 million dollars was raised – generosity abounded.

While Alisa, Rashad, Dan and I were relishing the gala, where JDRF head Arnold Donald among many others gave a very moving speech, John and Jenny were in Barcelona, soaking up Gaudi and pre-diabetes (in reverse order), at the 2<sup>nd</sup> Annual Congress on "Prediabetes" and the Metabolic Syndrome, Epidemiology, Management, and Prevention of Diabetes and Cardiovascular Disease. This meeting, which drew 3,000 healthcare providers and researchers and professionals from around the world, had one of the best faculties we've ever seen put together (ever) – the density of brainpower was off the charts. The focus was the hottest topics in pre-diabetes and prevention – see our story inside about the global crisis and what we saw as the top five themes: 1) Waist circumference is the best proxy for visceral fat, so whip out your measures to find the most at-risk individuals; 2) Metabolic syndrome as a syndrome is here to stay but be sure to recognize differences in relative vs. absolute risk – the latter must still be measured to assess an individual's likelihood of CVD; 3) As you would imagine, obesity was top of mind but exercise was actually bigger than weight loss – as a society, it was pointed out, we're faced with the choice of activity or inactivity – or to put it more plaintively, health or healthcare; 4) Ethnic variations are big and complicated and are hitting the developing world harder than we can imagine; 5) Discussion about prevention of diabetes was decidedly not on drugs but about lifestyle intervention, with metformin coming in here and there. It was too early to discuss new meds in our view – but also in our view, there wasn't enough recognition of how the old medications don't work. We wish the US were like Denmark, where everyone rides bikes everywhere ... alas, we fear, we have miles to go.

Stay with that thought. With all the treatments for type 2 diabetes, have you ever thought about what you would do if diagnosed? This issue came up at Dr. David Klonoff's Diabetes Technology Society meeting last week in San Diego, where only 8% of the audience reported prescribing Byetta for initial therapy (it is off label, after all) but where nearly 40% said they would prescribe it for themselves as first-line therapy if they were diagnosed. We considered what this might mean for the success of a drug — what the experts say they'd use to treat themselves. The consideration disregards many important practical considerations, of course: cost, reimbursement, marketing, label ... But we think for the long-term, it's really quite telling. As limitations are stripped away, and as applications become easier (read: LAR, liraglutide), isn't it likely that penetration would approach the number of clinicians that think it's the best?

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And sobering to think about: even if penetration were, say, a tenth of that, this would approach a \$5 billion market.

We were impressed by some new data at the clinical therapeutics meeting – results from STAR-2, a two-center pilot study comparing MDI and the Paradigm REAL-Time system. MDI caused a one-point drop in A1c, and the combination of continuous monitoring plus pump therapy caused a two-point drop, both to around 7.5%. Starting A1cs were different due to randomization and n (=30) was small, but the point was to determine the feasibility of the training program proposed for switching pump-naïve patients onto the Paradigm pump for STAR 3, a prospective, randomized study that has now begun. We learned at this meeting that CGM actually makes fingerstick data more useful, a type of synergy that we increasingly see in devices – sensors to augment pumps, PDAs to augment meters... All this data is integrated with newer software in order to provide the most complete picture of a patient's management profile.

-Kelly L. Close

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#### Quotable quotes from April's DCU inside

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.

- April 30: Was Gina Kolata in Barcelona? The NYT on waist circumference
- April 19: A new area of medicine decides what it means to live well
- April 17: You want a Revolution? Steve Case has started one.
- April 12: Weighing in on the stem cell type 1 research Dr. Skyler speaks
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# Besides writing our own blog, we also write a blog for Revolution Health called "Up Close and Personal" on life with diabetes. You can find it at <a href="https://www.revolutionhealth.com/blogs/kellyclose">www.revolutionhealth.com/blogs/kellyclose</a>.

- April 22: Michael Pollen Doth he protest too much? Today's NYT and his urge to vote with your forks ~
- April 12: Exciting (if early stage) results in type 1 diabetes with stem cell transplantation
- April 9: Is diabetes a condition or a disease? (Or, want a way to start a heated argument?!)

#### Coming soon in DCU...

- Conference highlights from AACE and the Clinical Diabetes Technology meeting
- ADA conference preview

#### TheLongerVersion

#### 1. Quotable Quotes from April's DCU and the Wider World

Dr. Richard Hellman, President, AACE, in April's DCU on the crisis in endocrinology and what would help diabetes patients the most:

- "I would maintain that for a young doctor who is idealistic about caring for people, taking care of people with diabetes is a wonderful pursuit, is extraordinarily interesting, these are wonderful times for it, and it's something that they should consider very seriously. One of the things I intend to do as president of this organization is try to interface with everyone who will help me carry that message forward, and it looks like the first one is you... So please quote me on that. I really do intend to reach out to medical schools and I intend to visit some and I'd like to have others of my colleagues visit others to make the case to the young medical student that they may not be getting the full picture."
- "Even the technology of glucose sensing, which I think will one day revolutionize the field of care, is probably not as central as some of the fundamental understanding that people don't yet have. People are undereducated. There's an assumption that if you learned it 15 years ago you still have it. There's the assumption that your thinking doesn't change with illness concomitant illness. All of those assumptions are wrong and people don't understand back-ups."

Dr. Louis Monnier, Montpellier, France, on Dr. Steve Edelman's dose-escalation trial of pramlintide as adjunct therapy to insulin in type 1 diabetes:

- "I was profoundly disappointed, however, by the lack of improvement in HbA1c levels when pramlintide treatment was compared with placebo, as well as by the absence of data on two of the main markers of diabetic control—fasting plasma glucose levels and variations in glucose concentration (the latter is a potential risk factor for vascular complications)."
- "In conclusion, the reader is left with a very mixed impression of the overall treatment effectiveness of pramlintide... For the moment there are no evidence-based data to justify the clinical use of pramlintide (at either fixed or progressive doses) as an adjunct to insulin therapy in type 1 diabetes."

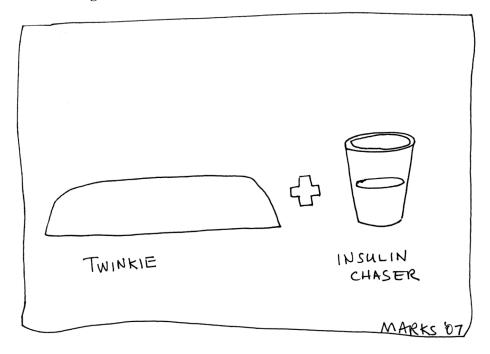
Drs. Paul Jellinger, Harold Lebovitz, and Jaime Davidson on behalf of the ACE/AACE Outpatient Glycemic Control Implementation Task Force, on the ADA/EASD Consensus Algorithm for Type 2 Diabetes:

- "A philosophical problem is the rejection of the value of newer, well-proven treatments because they lack multiyear clinical trials. This has the potential result of depriving diabetic patients the benefits of new and unique agents for years."
- "The failure to emphasize the importance of postprandial glucose in achieving A1C targets in the algorithm limits its ability to help patients reach glycemic goals."

Dr. David Nathan on behalf of the ADA/EASD Consensus Group, in reply:

• "The consensus group used effectiveness in lowering A1C as the primary criterion for judging the available medications, giving more weight to long-term than short-term studies. Secondary considerations included safety, side effects, tolerability and patient acceptance, other factors that might reduce complications independent of glycemia, and cost. Using these criteria, the consensus group was not persuaded that any of the new medications should be included in the algorithm at this time."

#### 2. diaTribe FingerSticks



—by Benjamin Marks

# 3. DCU Company Watch

- Sanofi-Aventis—FDA approved new Lantus SoloStar disposable pen: On April 30, the FDA approved the Lantus SoloStar pen, which will be made available in US pharmacies this year. This disposable pre-filled pen is the only pen that can dose up to 80 units with a single injection (for insulin resistant type 2 patients). It also requires 30% less "injection force." according to a Sanofi study in March's Expert Opinion on Drug Delivery. This benefit helps patients with limited dexterity and mobility. Before the SoloStar, Lantus could be delivered in the refillable OptiClik pen or with a vial and syringe. The OptiClik, however, had various delivery problems, so it's great to see this new product and we'll be waiting to hear how patients like it – and whether it is covered by their insurance. Also recently approved in Europe along with the Apidra SoloStar, the Lantus SoloStar was made available in Germany on April 2, with a French launch set for May. It launches in the rest of Europe in the next 12 months. SoloStar will be the only pen that color codes based on insulin type – gray for Lantus and blue for Apidra. According to our best industry sources, pens now account for about 15-16% of all units of insulin delivered in the US, but are said to have penetration well above 80% and 90% in Europe and in Japan. In the US, a higher percentage of pens are disposable. suggesting that – Al Gore's An Inconvenient Truth notwithstanding – American consumers are willing to throw away their hardware.
- GlaxoSmithKline 1Q07—Oh-so-robust quarter for Avandia: The quarter was a resounding success for the Avandia franchise, with sales of \$818 million up 19% year-over-year. Although the increase was just 3% sequentially, the company did have a tough comparison. US sales rose 19% and robust international sales rose 37%. We had more evidence that combination therapy really is coming Avandamet (combo of Avandia and metformin) comprised 20% of sales for the franchise in the quarter, up from 7% last year. If reimbursement progress is good for combination therapy (a whole new frontier), we see combination use with exenatide being quite positive for Avandia. Management attributed

success to resolved supply issues and to ADOPT, which has excited reps at meetings. For now, we believe DPP-4 inhibitors are doing more to expand the market than to take market share from TZDs. Management noted its belief that Avandia is taking shares from sulfonylureas as well as from Takeda's Actos. Asked why management took so long to disclose issues with TZDs, it defended its response, which we have to say, did seem pretty timely. Management went out of their way in his introductory comments to mention Alli, the OTC version of Xenical, which will launch in June – that was interesting to us, and we are thinking that prospects for this are higher than we had imaged.

- AstraZeneca 1Q07—Tidbit on BMS agreement and no other new news: The AstraZeneca call was quiet on the diabetes front R&D did increase 36% and one reason cited was the BMS diabetes collaboration see below for more on this program, in which DPP-4 inhibitors and SGLT2s are the focus.
- Novo Nordisk—Two hundred million on the Brazilian insulin plant: Novo inaugurated an expansion of its Brazilian insulin plant, which is evidently the largest single pharma investment in Brazil ever \$200 million. The facility will be 37,000 square meters, with the most advanced insulin formulation and filling technology available globally. By year's end, Novo will have 750 employees there (from 400). The plant will formulate and fill insulin into standard Novo three-milliliter cartridges, currently used in all its pens. About 95% of the pens will be for export to Europe, Canada, Australia/New Zealand, and some developing countries. In addition, Novo recently approved \$50 million to construct a facility to manufacture the FlexPen in Brazil, the plans for which will be finished by 2009. FlexPen is the most popular pre-filled pen in the market. This investment is more evidence of Novo's powerhouse sales it reports first quarter results later this week (May 2), and we're curious to see where they come out on revenue and pipeline news.
- Amylin/Lilly—Byetta rolled out in Europe: Byetta just launched in Germany and the UK, slightly ahead of schedule; Scandinavia will follow shortly. Lilly hopes to launch the drug in over 30 countries by year's end. The Reuters piece begged for controversy, noting that Byetta is expected to face competition from Januvia and Novo's liraglutide we would say how great it is that all the countries have more choices! That said, Merck is on a roll with Januvia, which is now approved for use in 47 countries the company has moved fast.
- Bristol-Myers Squibb 2Q07—Shifting into metabolics with Pfizer and AstraZeneca agreements: Diabetes is SO in the news! BMS released a new agreement with Pfizer on preclinical metabolic compounds, in which Pfizer will cover all research and early-stage development and the companies will jointly work on phase 3 development and commercialization. This seems in line with BMS' strategy to partner on "high unmet needs," share more risk, and focus on new targets cost-efficiently. BMS will pay Pfizer \$50 million up front and will share all development and commercialization expenses 60%/40%. Pfizer pays the larger share and gets more profits. This partnership is in addition to BMS' partnership with AstraZeneca to work on all compounds in two classes – DPP-4 inhibitors and SGLT2 inhibitors. DPP-4 inhibitor saxagliptin and SGLT2 inhibitor dapagliflozin are the two late-stage compounds in development. Data on both will be presented at the ADA meeting in June – some phase 2 and phase 3 data for saxagliptin. Yes, if you wondered, this means these classes are off-limits to Pfizer. And likely off-limits to anyone looking to snap up BMS – this would make the company a little less attractive to acquire, we would assume. We suppose in some respects it may ultimately make it *more* attractive to Pfizer and/or AZ. In Q&A, it became clear that BMS was intentionally shifting away from primary care markets into more specialty markets, with these two metabolics deals – on the other hand, it's becoming increasingly clear that diabetes is anything but a specialty market.

- Sanofi—Rimonabant approved in Brazil: Acomplia was approved in Brazil on April 25. We are becoming more and more interested in what will happen at the FDA Advisory meeting on June 13 we also wonder who is on the panel, since we assume no one who worked on the trials could be, due to the FDA's new rule on this (which we would characterize as overdone don't we want the best educated doctors on the panel? And while there is always room for abuse, is this really the right way to enforce it?) Acomplia got surprisingly little mention at the pre-diabetes meeting in Barcelona, which was extremely evidence-based and thus focused primarily on the older drugs for diabetes prevention: metformin, acarbose, and to a lesser extent or listat and TZDs.
- **BD 2Q07**—**Glucose monitoring business sold to CSC Medical for a song:** US Diabetes Care revenue grew 6% this quarter year-over-year, and the total Diabetes Care revenue grew 5% year-over-year. There was said to be good growth in insulin delivery supplies, probably due to pen growth from Byetta and Lantus. The blood glucose monitoring business was sold for a mere \$20 million, well less than a 1x multiple to CSC Medical. Tough negotiations were likely part of this one.
- Active Control—Seeking FDA clearance for in-hospital glucose control product: Active Control, a newly incorporated Delaware company based in San Jose, CA, specializes in ICU products that can reduce time of stay and mortality rates. It announced April 24 that it had begun private fund raising efforts to develop "The Rule," its product for glycemic control in hospitals. The product was licensed on March 19 from Intersection Lifesciences Ltd, a New Zealand company, and is currently under a 510(k) filing review at the FDA. Active Control is looking for hospitals in the US to pilot the technology, which monitors patients in the ICU and uses a slide rule to recommend patient-specific nutrition and insulin doses to healthcare providers in order to maintain tight blood glucose control.
- Novartis 1Q07—Quiet on Galvus, little positioning on the approvable letter: In Novartis' April 23 call, there was no assurance on Galvus, and little mention in the prepared remarks except that the delay was not a positive. We'll hear a European response in 3Q, which management did not sound particularly optimistic on we assume this decision will come to a screeching halt without the US approval. A meeting with the FDA on next steps is imminent, but we aren't sure where this falls in terms of all the meetings with the agency. In general, the approvable letter was positioned as bad news, with no effort toward a bright side. No one uttered the word "Januvia." We see this as mostly positive but a bit mixed for Januvia certainly positive for Januvia in that it doesn't have to compete with another DPP-4 inhibitor, but negative in that it raises more questions about the class. There was no news on GLORIOUS and GALIANT trials. As a reminder, GLORIOUS is the program of five major outcomes studies for Galvus, and GALIANT is the 90-day head-to-head study versus TZDs now ongoing. On the latter, even if it is positive (it is designed to show non-inferiority to TZDs), we believe it will be criticized as too short; indeed, it does often take three months for TZDs to show effect.
- Pfizer 1Q07—Pfizer lowers expectations on Exubera for 2007-08: Pfizer reduced expectations for the drug at least through 2008. It also acknowledged the need for more support in using the "novel delivery device" we think the hassle factor has been a key barrier to date, and while PCPs definitely seem more open to inhaled insulin and less worried about safety, they also are more stretched for time. We also understand the marketing team continues to change for the inhaled insulin franchise, and we're cautious about forecasting success on the DTC front direct-to-consumer advertising is supposed to begin in the second half of 2007. We thought the last line of the Exubera paragraph in its press release was especially muted: "We will continue to monitor the performance of Exubera..."

- Merck 1Q07—Januvia pulls in \$87 million in first full quarter: Merck's 1Q07 estimate of \$87 million in Januvia sales was more than double last quarter's number of \$43 million. In that first quarter on the market, Januvia sold \$43 million in 10 weeks; this quarter was nearly 13 weeks, so the comparison will look quite good. Management said on the call that it expects that Merck will be able to do more to help patients with type 2 these numbers by the way don't include Janumet, which was approved March 30. Comparisons to Byetta are inevitable at this point we would point out that the sales strategy clearly was very different; the doctors being marketed to as well as the target patients were different in the early stages. For Merck, safety is still a big issue, as is longer-term efficacy. On the other hand, the company already has Janumet approved, which is faster than expected. One other item of note is that its SG&A looks to have increased only 5% year over year, which we would term quite impressive given the expected launch of this product.
- Roche 1Q07—BGM growth 11% globally to \$626 million; GLP-1 timing still 2010 for submission; working on auto-injector device: Roche reported very positive diabetes care results April 19, with revenue over \$600 million and overall growth at 11%. Blood glucose monitoring rose 10%. Management several times referred to a "renewed" Accu-Chek portfolio. North American growth in particular was noted for being stronger than expected. Pharma results also noted below – we continue to believe that GLP-1 is prompting less frequent blood glucose monitoring and so note Roche's work in this class – it is not expected to market before 2010-2011. Blood glucose monitoring revenue was ~ 700 million Swiss Francs, or ~\$580 million globally; this reflected growth for the first quarter of 10% - very strong given all the industry pricing pressures. Insulin delivery revenue looks to have come in at roughly \$45 million, surprisingly strong. Local growth in pumps was 21% versus a year ago (up from 11% year over year growth last quarter) – no growth given for the US, since it was \$0 a year ago due to the ban. The company has one new product that is being released this year globally called the Accu-Chek Performa, where the focus is five-second results, extensive quality checks, and advanced data management features. The successful Accu-Chek Compact will have a new user interface and "more attractive" ergonomics – we assume this means smaller/more portable – this is the "drum" meter, of course. There was no update in terms of planned product submissions for diabetes drugs in phase 2; R1583, its GLP-1 is still listed for planned submission in 2010. The company noted which compounds would have updates at medical meetings in the second quarter, and this wasn't listed (nor were any diabetes drugs). Interestingly, management said it is looking at an auto-injector device for administration for the GLP-1 - this is not a Roche device, but executives "couldn't remember" the supplier when asked. The volume and needle size for this may be bigger than expected – the market has been obsessed with this question regarding Amylin's LAR, which is expected to be approved in 2009. There were no changes for other drugs in phase 2 for diabetes, including R1439 (not disclosed what sort of drug) or R1440, its GKA; or R1658, its CETB inhibitor for dyslipidemia, The company doesn't have anything in phase 3 and didn't comment or show a slide on phase 1. On R1658, Roche did reiterate last quarter's plan that it would take a decision this year whether to move to Phase 3, and this would be based on full data review on the class and regulatory discussion. Xenical sales fell 24% in Europe and 7% in the US during 1Q - during 2006, Xenical global sales were CHF 680 (\$564 million) in 2006, and CHF 635 (\$526 million) in 2005, an increase of about 7%. Given all the problems with Xenical and Merida, it seems incredible to think that the two together would still roughly qualify for blockbuster status, at least as of last year's sales. We understand from clinicians that all the focus on rimonabant last year did drive some patient interest in these two compounds. One slide showed the lifecycle management for Xenical - Alli, the OTC, has been launched by GSK (no word on this) and the non-RX sales outside US were also outlicensed to them.

- Abbott 1007—BG sales decreases in the US offset by international growth: No-coding FreeStyle Lite meter approved: Diabetes Care growth was modest at mid single digits worldwide – just over 4% year-over-year growth to \$285 million. In the US, sales fell 5.8% year-over-year to \$131 million from \$139 million. Internationally, sales increased ~7% yearover-year to \$154 million not including the exchange rate (with a positive impact of nearly 8%). Management expects a return to double-digit growth in 2H07. On Navigator, management said only that the product was in active regulatory review and that approval would be in the coming months. The approval of the FreeStyle Lite system was highlighted; Abbott announced April 16 that the FDA had approved its FreeStyle Lite, a no-coding meter. It's modeled off the FreeStyle Flash, but interestingly, it won't replace it, at least not at this stage, according to media relations. From what we can tell the main difference is the addition of "no coding." New head of diabetes care at Abbott, Chip Vance, emphasized simplicity and ease of use in his press release. It seems to us like there was a fast turnaround at the FDA for this meter. Abbott wants to launch the meter in May, which will likely be a "soft launch" prior to ADA. Management said that neither Roche nor LifeScan offers devices that autocalibrate – as it often is in technology, Bayer was the leader on this front, first offering a nocoding meter in 2004. Jane Seley, the noted diabetes educator from New York Presbyterian-Weill Cornell Medical Center, praised the meter for its "killer combination" of no-coding and smallest drop size and excellent backlight and said it made a big difference in terms of speed and convenience. Management also said that it's developing its fully integrated BGM device with test strips, lancing, and meter -- this would be an updated Sof-Tact, we assume, but there was no new information from last quarter.
- Arena 1Q07—Lots of interest but no new news on lorcaserin: Almost every question—and there were many—at Arena's 1Q07's earnings call was on lorcaserin, Arena's antiobesity compound in phase 3. Management was reassuring but did not provide many new details. A February completion of the BLOOM trial, the major pivotal phase 3 for lorcaserin, was a key development this quarter and two additional trials are expected to be initiated soon, all to be completed at NDA filing in 2009. Arena will partner it somewhere in that timeframe. There were many questions about the safety of lorcaserin, with investors fearful of valvulopathy, the condition that took fenfluramine and dexfenfluramine off the market years ago. Management discussed lorcaserin's "spectacular" specificity as well as the structured review of echocardiographic safety data throughout trials. Data from the first review will be key to the survival of the compound and are expected in September. Elsewhere in diabetes, results from a series of phase 1 trials for APD668, Arena's GDIR (Glucose-Dependent Insulinotropic Receptor) compound for type 2 diabetes partnered with Ortho-McNeil should be presented by J&J this quarter or next. It activates glucose-dependent insulin secretion and incretin secretion through a double mechanism and is an oral drug.
- J&J 1Q07—LifeScan reports low US growth offset by higher sales globally: J&J reported earnings on April 17 in a call that was very light on diabetes and obesity overall nothing about continuous monitoring or really diabetes in general. Total LifeScan sales reached \$549 million for 1Q, up 6% globally on a reported basis and 9% including the currency benefit. Excluding Animas, we believe LifeScan growth was likely around 5% on a reported basis. While both figures reflect records for the geographic areas at LifeScan, they aren't large increases from Q4 (\$3 million and \$4 million, respectively) i.e., some percentage of Animas growth is "incremental" since a full quarter of Animas growth wasn't reflected in the 1Q06 numbers. In 1Q, US sales in LifeScan were \$292 million, up 1% from a year ago although this is actually \$3 million more than 4Q US sales of \$289 million in absolute dollars; the low percentage growth reflects that Animas growth is now "annualized." Excluding Animas' contribution, we believe LifeScan growth may well have been negative, likely down 3-5%. International sales reached \$257 million in 1Q, up 12% from a year ago (19% including a

currency benefit) – this result marks the second quarter-million sales mark for LifeScan for international sales. However, excluding the international Animas sales, "actual" growth would likely have been a few percentage points lower, in the range of 5-10%. As usual, Animas growth wasn't reported, but we believe sales were likely on the weaker side both due to stronger competition and since patients would have been waiting to get the 2020 – perhaps in the area of ~\$20-25 million. No comments were made on LifeScan except for crediting the OneTouch Ultra for growth at the company. No comments or questions were made on LifeScan or Animas. J&J did submit to the FDA its gastric band product Endo-Cutter (which will compete with Inamed's Lap-Band) to treat morbid obesity. This is long awaited. The product was characterized as a strong growth driver overseas. On the pharma front, there was no update on the Ortho-McNeil collaboration with Metabolex.

- Sanvita—NovoMAX no-coding meter under FDA review: There was another new no-code meter at AACE called NovoMAX, made by Sanvita, not approved by the FDA yet. This is a new company, which is replacing the BD strips. Sanvita is a home distribution company, trying to benefit from competitive bidding changes. The meter is this nice little blue object, pretty hip-looking, though the buttons may be considered small for elderly or vision impaired patients. The company apparently submitted the filing to the FDA in December 2006, with routine 90-day evaluation, and is expecting approval "any second now." Sanvita shared that it was actually hoping it would get approval before AACE, but it didn't happen clearly the ROI would've been higher on the conference otherwise. The company is coming out with a new meter because it wanted a branded meter to go with its strips, but it thinks this meter, NovoMAX, stands on its own merits: no coding, 4 second test time, and 0.3 uL samples, which seems pretty impressive though we weren't able to try it at AACE because it isn't yet approved.
- Amylin 1Q07—Strong revenues of \$162 million: Amylin reported strong revenues on April 16 of \$162 million. Byetta sales in 1Q were \$146.5 million, up nearly 7% from \$137 million in Q4 and up 114% from \$68 million a year ago. Compared to the 4Q06 call, sampling was de-emphasized and CEO Dan Bradbury gave several reminders to investors that Amylin has many other marketing initiatives underway, including medical education, which may yield more potential long-term growth than sampling. Symlin sales in 1Q were \$15.5 million, up a healthy 14% from Q4 and up 104% from \$7.6 million a year ago. This compares favorably with growth in Q4, when quarter-over-quarter growth was 9.7% and growth over last year was 109%. As has been the case since Byetta was approved, there was virtually no discussion of Symlin on the call. We continue to believe that although it's a complicated drug, it's also a sleeper drug. Net loss for Amylin was \$49 million. CFO Mark Foletta reaffirmed previous guidance for 2007. The LAR trial is expected to report in 4Q; management said that LAR will be administered through self-administered subcutaneous injection with a small volume the volume point is important as it suggests fewer injection-site reactions. On the Integrated Neurohormonal Therapies for Obesity (INTO) front, Amylin has several studies ongoing:
  - o its pramlintide plus leptin proof-of-concept study is fully enrolled with results in 2H07;
  - a pramlintinde and PYY safety and tolerability study has completed Amylin
    will not report the results from this study, as it was only a preliminary study it
    wanted to undertake before doing a larger triple-therapy study of pramlintide,
    PYY, and leptin;
  - o its second-generation amylinomimetic continues in phase 1 program, which is expected to continue into 2H07; and

o a phase 2b trial for pramlintide plus phentermine and sibutramine is fully enrolled, and results are expected in 2H07.

Amylin has a lot planned for ADA – we note a big win that incoming ADA president Dr. John Buse will do one of the company's two Byetta oral presentations. Overall the company will have four orals, eleven posters, and five publish-only abstracts. The only mention of Januvia was in Q&A, when management said that it believes the introduction of Januvia has really been focused on replacing SFUs and TZDs, and that Januvia is being used earlier in the continuum of care than Byetta in the majority of cases. We think Byetta would be very helpful as first-line therapy and look forward to seeing data on this front.

- Lilly 1007—Good quarter in diabetes, thanks to Byetta (and price increases): The Lilly call started 30 minutes after the Amylin call on April 16, and these two companies pretty much opened earnings season this quarter. Lilly has raised guidance for 2007 from 'high single digits to low double digits.' Diabetes Care sales rose 11% to just under \$340 million. Without Byetta and Humalog growth, Lilly's diabetes franchise would be in trouble – Humalog growth alone could not have offset the Actos drop and the relative Humulin weakness (\$226 million in 1Q07, which is up 3% from \$219 million in 1Q06 but down 12% sequentially from \$257 million in 4006). Price increases in major products also helped. Humalog saw a year-over-year increase in U.S. sales of 11% to \$340 million and international sales growth of 12% - quite respectable although we look for healthier gains from Novolog when Novo Nordisk reports sales this coming week. Humalog was hurt by other alternative insulin delivery systems but still had strong growth. Lilly has increased the diabetes sales force by 40% (it's a great time for good diabetes reps as Novo increased its sales force recently by 60%) and interestingly, the new reps will focus exclusively on Humalog – perhaps this is what Lilly was thinking of when it said last year it would be reenergizing its insulin franchise. Lilly's share of Byetta was \$72 million (total Byetta sales were ~147 million), an increase of \$36 million versus 1006. Management said it's now working through the point where sampling would have had a big impact on revenue. The European regulatory application for Arxxant for diabetic retinopathy was withdrawn, which is bad news for the company. We're assuming, sadly, it's probably DOA in the US, though we are still holding out some hope. In our view, the clinical development program appears to have been botched – while there are questions about the mechanism, the real problem was trial design and results. Lilly has several initiatives to expand use of Cymbalta for diabetic peripheral neuropathic pain (DPNP). A new group of sales reps are focused on this use in a specialist setting, and Lilly is increasing emphasis on DPNP in a primary care setting, including the use of new print ads.
- DiObex—Series B financing raises \$24 million for phase 2 trials: DiObex announced on April 16 the completion of a \$24 million Series B financing round led by Inventages Venture Capital (Switzerland). Other new investors in this round include Mitsui Ventures (Japan) and Pac-Link BioVentures (Taiwan). Series A investors Domain Associates, Pequot Ventures and Sofinnova Ventures also participated. DiObex indicated that the capital will be used to fund phase 2 clinical trials for DiObex's two leading drug candidates: DIO-901, VLD-Glucagon (very low dose glucagon) for the prophylactic treatment of hypoglycemia in type 1 diabetes patients undergoing insulin intensification, and DIO-902, an oral once-daily cortisol inhibitor for type 2 diabetes.
- Amgen—Successful Brazilian proof-of-concept study of Kineret for type 2 diabetes: On April 12, the *NEJM* published a highly profiled original paper and editorial on the results of a trial testing the recombinant human interleukin-1 receptor antagonist anakinra (Kineret) for type 2 diabetes. Anakinra, a peptide drug currently used to treat rheumatoid arthritis, is expensive at more than \$1,000 per month. In this 69-patient study, Dr. Claus Larsen and

colleagues demonstrated that 13 weeks of treatment with anakinra improved beta-cell secretion and A1c in patients with type 2 diabetes. IL-1R antagonism represents a novel mechanism for treating type 2 diabetes by possibly rescuing beta-cell function or delaying beta-cell apoptosis. While this is a small study that needs to be followed by dose-titration trials and larger, longer-term studies, we think it shows that anakinra or other more longacting IL-1Ra's could represent an important new class of drugs for treating hyperglycemia and delaying progression of diabetes. In an accompanying editorial, Dr. Kristina Rother of the NIDDK discussed how these findings are a reminder that type 1 and type 2 diabetes share some of the same beta-cell pathologies; she suggests that reducing glucolipotoxicity-induced beta-cell stress probably helps for any type of diabetes. She goes on to speculate (against the authors' own conclusions) that reducing inflammation and thus peripheral insulin resistance probably played a role in anakinra's effect. She notes that anakinra fits into the future paradigm of diabetes treatment, which will include treatments that improve beta-cell function in the long term (she cites exenatide and sitagliptin as potential such drugs) as well as hyperglycemia in the short term. She cautions, however, that the A1c-lowering efficacy in this trial was small, and long-term data are needed on anakinra for diabetes.

- Pfizer—NYT's Alex Berenson weighs in on inhaled insulin: NYT reporter Alex Berenson wrote an article on April 10 entitled, "Exubera, the first and so far only commercially available inhaled-insulin diabetes treatment, is on the verge of turning into an expensive failure for its maker, Pfizer." The story isn't about new news *per se*, but Berenson quotes a number of Wall Street analysts who have reduced estimates, and he also mentions Byetta's success (as well as noting Symlin). He makes a favorable comparison to Januvia (for Merck) at the beginning of the article, noting that the DPP-4 inhibitor is prescribed about 25 times more commonly than inhaled insulin. Dr. John Buse is quoted: "Out of 2,000 times or more I've tried to start patients on insulin, I've only been turned down twice," said Dr. Buse. Lilly gets a nod as far as next-generation inhalers go, though Berenson's overall impression seems to be that inhaled isn't really a "go" not just the Pfizer product due to broader, oft-discussed issues like reimbursement, potential safety problems, etc.
- DexCom/Abbott/Medtronic—Preliminary HCPCS codes for CGM granted: DexCom, Abbott, and Medtronic received preliminary HCPCS (Healthcare Common Procedure Coding System) codes on April 9 for continuous glucose monitoring (CGM) technology. Public discussion on this preliminary decision is scheduled for May 1-3 and publication of final decisions will likely come at the end of 2007 with implementation of the codes in January 2008. As a reminder, HCPCS codes are necessary for Medicare, Medicaid, and other insurers to track process medical coverage requests. DexCom and Medtronic's request for HCPCS codes was denied last year because of insufficient demand.
- Metabasis—Phase 2a study for gluconeogenesis inhibitor MB07803 initiated: Metabasis announced April 4 that it had begun enrolling a phase 2a trial for MB07803, its second FBPase inhibitor candidate. Metabasis' first FPBase inhibitor, CS-917, was licensed to and is now being developed by partner Daiichi Sankyo and is currently being evaluated in a 392-patient phase 2b study. Results from that study are expected in mid-2007. Metabasis is developing MB07803 independently. Both compounds inhibit an enzyme necessary for gluconeogenesis called fructose 1,6-bisphosphatase (FBPase). They work primarily by decreasing the high levels of liver glucose output seen in patients with type 2 diabetes. The phase 2a trial for MB07803 will enroll 60 patients with type 2 diabetes and test four different doses of the drug versus placebo over 28 days of treatment. Metabasis reports that phase 1 trials showed MB07803 to be safe and well-tolerated, with only mild adverse events and no withdrawals from adverse events.

Novo Nordisk—Personalizing and diversifying patient education website: Novo updated its Changing Life with Diabetes patient education website on March 29. For us, this renovation reflects the diabetes drug giant's position as a catalyst for change. The new site is also part of the growing trend toward direct-to-consumer marketing in diabetes, with the Internet catching a lot of the action: Medtronic Diabetes Care just launched a new site as well, and we assume other companies will follow suit. As with Medtronic's site, Novo's is focused more on education than on selling any particular product – in fact, the amount of information provided, specifically about insulin, is comprehensive to the point of overwhelming. What struck us most, however, was the site's effort at personalization and diversity. Patients can create a personalized home page to construct a "Diabetes Care Plan" – they have to "sign in" and become members, then fill out a series of questions for both their daily goals (glucose testing, physical activity, etc.) and long-term goals (weight, A1c, etc.). While we found aspects of the navigation somewhat confusing or redundant, and while initially not everyone will want to take the time to sift through the pages, fill out the healthrelated numbers, and keep updating their information, we do believe the site will be most useful to highly motivated patients. In terms of diversity, the site comes up in English, but it's also available in Spanish – and likely other languages to follow. Overall, the new site is one more weapon in Novo's marketing arsenal – something that's sophisticated if a bit complicated, but delivers a message of inclusion and compassion.

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

4. International Diabetes Federation issues consensus statement on diabetes prevention at 2nd International Prediabetes Congress, April 25-28, Barcelona, Spain, <a href="http://www.kenes.com/prediabetes">http://www.kenes.com/prediabetes</a>

The 2nd International Congress on "Prediabetes" and the Metabolic Syndrome drew about 3,000 doctors and researchers from around the world to Barcelona to talk about the hot topics in prediabetes and prevention. We thoroughly enjoyed this meeting, which assembled one of the finest groups of speakers we've ever seen. The overall tone was one of urgency but not despair: everyone noted that prediabetes and metabolic syndrome are becoming a global crisis, and that they will be difficult to combat, but they seemed to think it was possible. Below are our five major themes for the conference, followed by a therapy-by-therapy summary of current thinking on various treatments for preventing diabetes and CVD, and the IDF's new official guidelines (released at the meeting on April 26) on diabetes prevention.

#1: Measure waist circumference! It is our best proxy for visceral fat and is absolutely the best way to find at-risk individuals. If there was one thing that everyone agreed on, it was the importance and power of measuring waist circumference. The IDF criteria for diagnosing metabolic syndrome were applauded for their emphasis on abdominal obesity as the primary criterion. The doctors we talked to all thought that their biggest takeaway for this conference was the need for every single HCP to have a tape measure in their office – and to use it on all patients. Needless to say, the science is very clear that abdominal obesity is bad: visceral fat causes diabetes and CVD while subcutaneous fat, if anything, is good because it stores excess energy in metabolically inactive tissue. Barring an expensive CT or MRI scan, waist circumference is the best way to gauge visceral obesity. A fasting triglycerides test adds an extra level of predictive value – a high value distinguishes the viscerally obese from the subcutaneously obese – but it's only an add-on and is impractical in developing countries. Waist circumference should be our primary gauge of risk.

#2: Metabolic syndrome only tells patients about relative risk – you still have to measure absolute risk to assess an individual's risk of CVD. There wasn't very much debate about the utility of the metabolic syndrome – all of the speakers accepted that it was a clinically useful way

of identifying high-risk individuals, particularly individuals who do *not* come up as high-risk on traditional risk calculators such as the Framingham risk score. In general, having metabolic syndrome doubles your risk of CVD, but if you have low risk to begin with (non-smoker, normal blood pressure and cholesterol, no family history, etc.), you're still better off with metabolic syndrome than someone with high traditional risk factors and no metabolic syndrome. Dr. J-P Despres emphasized that metabolic syndrome is only one of the "building blocks" for calculating global cardiometabolic risk, the others being high LDL/HDL, hypertension, diabetes, older age, male gender, smoking, and genetic susceptibility.

#3: Lots of discussion about obesity, not much discussion about weight loss. While doctors seem to believe diabetes prevention is possible (see below), the outlook on obesity prevention was less positive – when it was discussed at all. With lifestyle intervention, people can significantly reduce visceral obesity without much reduction in overall weight, so it was suggested that maybe we should stop thinking about weight loss and just think about visceral fat loss. Weight loss drugs were not mentioned much, due, we think, to their poor efficacy for those approved and to uncertainty or early stage of development for those unapproved. Orlistat (Roche's Xenical) was noted for its ability to reduce the risk of diabetes, but sibutramine (Abbott's Meridia) and rimonabant (Sanofi) were hardly mentioned. The upcoming FDA meeting during which we'll hear experts discuss rimonabant was also not mentioned much. The conference ended with a talk from persuasive Canadian architect Professor Avi Friedman, who engaged the audience with a dynamic and detailed description of how modern suburban communities promote inactivity and obesity. He then described the kind of living communities we should be constructing in order to promote more active lifestyles among the populace. Friedman presented Bois Franc, Quebec, Canada as an excellent example of responsible community design. Medium density housing faces squares; housing is for all age groups; pedestrian-oriented streets, sidewalks, and toddlers' play areas are in front of homes. There's a neighborhood commercial hub close to homes for shopping and public transit line connects the neighborhood to the subway system. Jogging and walking paths are common. As a society, Friedman pointed out, we're faced with the choice of activity or inactivity – i.e. health or healthcare.

#4: Ethnic variations are hugely significant, and diabetes is hitting the developing world hard. India and China have the most people with diabetes, with 31.7 and 20.8 million in 2000 (compared to 17.7 million in the US). Dr. Jean-Claude Mbanya, president-elect of the IDF, showed that among individuals of similar weight, Asians have the most visceral fat, followed by Caucasians and then individuals of African descent. For hypertension, Africans are the most vulnerable, followed by Asians and then Caucasians. As the IDF criteria for metabolic syndrome acknowledge, Asians and South Asians are prone to develop diabetes and CVD at much lower BMI's and waist circumferences than people of other races. Dr. Juliana Chan pointed out that lack of awareness and education about diabetes is a huge problem in China. Diabetic nephropathy is also more prevalent than in the US, causing as many health woes among diabetics as macrovascular disease.

#5: Diabetes prevention should be all about lifestyle intervention and metformin... maybe acarbose ... and in our view, testing the newest medications. Orlistat gets an honorable mention, but while everyone lauded the TZDs as effective, no one recommended them because of their side effects. Incretins, DPP-4 inhibitors, and rimonabant were hardly mentioned – which we found reasonable since this was a very evidence-based meeting and these is no trial evidence yet on diabetes prevention with these newer classes. Notably, every speaker on diabetes prevention cited the five major interventions that have been proven to reduce the risk of diabetes: lifestyle intervention (DPP and Finnish DPS and more), metformin (DPP), acarbose

(STOP-NIDDM), orlistat (XENDOS), and TZDs (DPP, DREAM). Here's the general consensus on each of these drugs, plus incretins/DPP-4 inhibitors and rimonabant:

- Lifestyle intervention needs to be taken more seriously both by healthcare providers and governments pretty much everyone agreed that lifestyle intervention should be first-line therapy. This doesn't mean we shouldn't use drug therapy, though, because there will always be people who can't or won't make lifestyle changes, and lifestyle won't prevent diabetes forever, especially in high-risk individuals. The attitude toward lifestyle at this meeting was completely different from that at US meetings, where diet and exercise are usually fairly summarily dismissed. The doctors here very much believed that with the right interventions and with societal/government support, lifestyle really does work we don't think the view from clinician leaders is that different in the US, but the confidence that societal/governmental support can emerge is. Exercise is the best of all drugs, if we can only get people to do it.
- Metformin was the favorite drug therapy for prediabetes based on the ADA/EASD recommendations for IFG/IGT. These recommendations were seen as progressive, in part because there isn't a label for prevention for metformin. Based on tolerability and safety and medical perception, metformin was by far the favorite drug option for preventing diabetes, and doctors seemed optimistic about its efficacy when it is used in combination with lifestyle intervention.
- Acarbose (Bayer) has potential in diabetes prevention and the ACE trial will look at this this is a large randomized trial of 7,000 people in China. Prediabetes and type 2 diabetes are diseases of postprandial hyperglycemia, so it makes sense to use a drug that targets postprandial hyperglycemia. We thought it was noteworthy that acarbose is not a commercially successful drug in the US, yet is being discussed as first line drug therapy for diabetes prevention in Europe. It sounded like the gastrointestinal (GI) side effects, while unpleasant, can be addressed.
- TZDs have good efficacy (DREAM, ADOPT) but were not recommended for prevention the side effects of edema, weight gain, and fractures were cited as problematic for a prophylactic drug as was the association with congestive heart failure. The only positive talks on TZDs were the ones in the GSK symposium, and even there the speakers seemed fairly objective and noted that the TZDs' side effects should be weighed against their benefits.
- Orlistat (Roche's Xenical) and sibutramine (Abbott's Meridia) were mentioned briefly a few times as preventive tools orlistat more than sibutramine, largely because of data from the XENDOS trial suggesting that it reduces risk for diabetes. Orlistat was called "diet in a pill" but not in a rose-colored way; its side effects are substantial and it didn't look like doctors were rooting for this to be included in any recommendations on prevention.
- Incretins/DPP-4 inhibitors, when discussed, were treated favorably but weren't really discussed for prevention. There just isn't any evidence (trials are just starting) for the use of these drugs in prediabetes. Lilly, Novo, Novartis, and Merck did all offer satellite symposia on incretins, however. In the Novartis symposium, Dr. Dan Drucker commented that combo therapy may be appropriate for prevention, since prediabetes is a multi-faceted disease, but cost-effectiveness will be important. Dr. Julio Rosenstock and Dr. Sir George Alberti both agreed that any future prevention trials should use metformin as an active comparator in addition to lifestyle modification in all trial arms.

• Rimonabant was mentioned surprisingly little – considering that it is approved in Europe, that this is a prediabetes conference, and that Sanofi has worked hard to position it as a cardiometabolic health drug. Dr. Stephen Bloom from the UK blasted it in his talk, and Dr. George Kunos of the NIH suggested that it may increase blood pressure in hypertensive patients. We didn't hear any cheerleaders for the drug, and we expect it could have a rough time at the FDA advisory meeting in mid-June at the FDA.

**Postview:** What the IDF has to say on prevention: In a consensus statement released April 26, the IDF encouraged governments to help prevent type 2 – primarily through lifestyle changes. It also supports the use of metformin and acarbose, though not TZDs, given safety concerns and side effects. The statement, which will be published in *Diabetic Medicine* in May, seeks to standardize national efforts to curb diabetes. The IDF is pushing this agenda hard, following the UN resolution, which in our view is an excellent next step as long as there are resources behind it. The consensus recommends three steps:

- Identification (for example, self-screening with questionnaires or opportunistic screening during doctor visits);
- Measurement of risk (a follow up FPG or OGTT test); and
- Intervention.

Initial intervention should be lifestyle – recommended exercise is 30 minutes a day, and recommended weight loss is two kilograms for the first month and 5 percent weight loss at six months. In order for lifestyle intervention to be successful, "serious societal changes" are necessary. Metformin and acarbose "should be considered" if lifestyle changes fail, but TZDs were not recommended due to side effects, despite positive trial results. According to the statement, rimonabant "shows some promise, but long-term safety [data are]...lacking."

—by Jenny Jin and John Close

#### 5. Interview with Dr. Richard Hellman, AACE President

Dr. Richard Hellman, MD, FACP, FACE, is the medical director of the Heart of America Diabetes Research Foundation in North Kansas City and a clinical professor of medicine at the University of Missouri—Kansas City School of Medicine. On April 14 he became President of the American Association of Clinical Endocrinologists for the 2007-8 year.

Dr. Hellman is a strong advocate a "back to the basics" approach, where the emphasis is on grounding patients in the essentials of diabetes care. He also favors intensive and comprehensive diabetes care; in 1997 he published a seminal paper titled, "Effect of intensive treatment of diabetes of the risk of death or renal failure in NIDDM and IDDM," which showed that an intensive treatment program reduced adverse outcomes in patients over a 14-year period.

We were pleased to sit down with Dr. Hellman at this year's AACE and ask him about some of his goals as AACE President, his perceptions of what needs to be done to address the diabetes epidemic and endocrinologist shortage (the topic of some research we are currently doing), and what diabetes patients really need most to improve care.

John: Thanks so much for spending time with us here in Seattle! We want to start off talking about some big picture topics. We're running a survey right now of medical students on their research interests, and we're troubled by their lack of interest in diabetes. We wondered whether you had also picked up this trend at the medical school level and what you thought could be done about it.

Dr. Hellman: I think you've hit the bell on the head. We've known that there was a problem in paradise for some time. There's a study a number of years ago, by Beckles and colleagues, where doctors in primary care were asked what kinds of diseases they least liked to take care

of and probably the three that came up were chronic low back pain, congestive heart failure, and diabetes. And diabetes was right at the top of the big picture ones. The reason was because it is a very time-consuming problem for the primary-care practitioner, and quite often the primary-care practitioner was the one who was seeing most of the people with diabetes. Even though an endocrinologist saw more patients with diabetes per person, there were a lot more of the others. And then the pressures for the doctors in managed care toward seeing patients more quickly worked against them wanting to take care of diabetes. To take care of a person with diabetes well, you need time and resources. You should have a team and you should offer coordinated care, none of which [is easy] as resources are being stripped away from the primary care doctor. And that has been filtered down to the medical students.

Moreover, we're very concerned that in the hierarchy of medical schools, the endocrinologist may be at the bottom of the totem pole, and often the monies in the department of medicine don't flow down as easily so there are many more despondent academicians in that area who then influence the medical student. Yet I would maintain that for a young doctor who is idealistic about caring for people, taking care of people with diabetes is a wonderful pursuit, is extraordinarily interesting, these are wonderful times for it, and it's something that they should consider very seriously. One of the things I intend to do as president of this organization is try to interface with everyone who will help me carry that message forward, and it looks like the first one is you.

John: Absolutely.

Dr. Hellman: There are plenty of opportunities for a clinical endocrinologist. It is not so difficult to form teams so you can have a group of people working together for care, and it's entirely doable. I should, in the interests of full disclosure, let you know that I was director of endocrine programs at a medical school a number of years ago, and I left the medical school because I felt that it might be more likely that I could do more innovation in diabetes care and get the kind of intensive and comprehensive care I thought the patients needed in the private sector. And we actually did a prospective cohort study, that we began right there, and we actually published our findings in 1997. It was widely cited, and I believe it was the first time, but not the last time, that someone had demonstrated both in type 1 and type 2 patients that a comprehensive and intensive form of therapy reduced death rates and kidney failure rates over a 14-year period. We had done that and what we had learned from that is that taking care of diabetes requires planning, thought, and organization, but it's entirely doable.

John: We're fully agreed with that.

Dr. Hellman: I'm preaching to the choir.

John: You are definitely preaching to the choir. However, there are some complications. Reimbursement is a problem, and it's hard for endocrinologists to build a practice and actually make money. A lot of people get reimbursed for doing procedures whereas as you just said, you need to take time, but there's no way to get that constant attention reimbursed.

Dr. Hellman: There is a change in my thinking on this. I had thought, when I began, and this is more than 20 years ago, that just simply doing the right thing was enough. I've learned now that in the world of managed care there are some plans that are so draconian – and that includes government plans like Medicaid – that you really cannot afford to offer the services. But fortunately there are still many plans – and I think Medicare is one, currently, at least for the moment – where it is possible for a doctor to give high-quality care, measure the care, so we're not trapped by our own belief that we're omnipotent or everything we do is right. I think it's important for us to both try and strive to do the best we can and then measure how we've done. I think both are important components.

John: You feel under those schemes it's possible to make money?

- Dr. Hellman: I believe that not all business arrangements and managed care contracts with doctors are business arrangements of a sort will allow people to be able to afford to deliver the services the patients need. I can't recommend, as an organization, that they look at any one and not another. You know, if I said that, we'd get sued, and I don't want to get put out of business by the feds. You can't do that. That's not legal and I would not try to. But I think it would be fair to say that in the 1980's I thought that we could take all comers and be able to deliver the same level of care. By the 1990's it was apparent that a physician in the private sector had to look, figure out how much it cost to deliver the kind of care the patient needed, and decide whether they could do it. But I would maintain that if people are well organized they can do that and earn a living. Perhaps I will not have a condo in Vail or out in the Caribbean, but I think that I can have a very worthwhile career. And that's the message I would give, that no, you can probably earn more money as a diagnostic radiologist and if that's what you want to do, please don't become a diabetologist but there are many other rewards that are important.
- Jenny: You mentioned broader issues like the healthcare system. If you could address the federal government on what it should do in the face of the diabetes epidemic, what would be your sound bite, your pitch to the government?
- Dr. Hellman: I'm not sure the federal government is the only important entity here. But the pitch I would make to all who would listen, or just the payors, is: it's in our best interests to prevent the complications of diabetes. The only way to do that is to invest in treating people early and intensively. There are data of all sorts. There are some beautiful studies with mathematical modeling that Dr. Bill Herman has done, and many other studies that show how early and intensive and comprehensive treatment could be very worthwhile. The government should invest in doing that and not create barriers, which they are now probably mostly inadvertently that are getting in the way by treating people with diabetes as second-class citizens and creating this spiral particularly for diabetics, but also for other chronic diseases so that for the person who's not well off, developing complications that interfere with their work is the first step in the spiral that takes them into poverty. Many of the bankruptcies in the United State are health-related, and the country needs to understand that we need to invest in our people, invest in the people who have diabetes especially, and invest in preventing it. They need to understand where their money should be put.

John: There's a lot of short-termism in the way they think about cost and benefit, isn't there?

Dr. Hellman: A lot.

Jenny: How do we get around that?

- Dr. Hellman: I think it's education and probably pressure. I think too often people have not worked together in a collaborative way. I would like to see more efforts from organizations that are not so much trying to raise money for themselves as trying to improve access for others. I think that probably is an important issue.
- John: If a patient were to speak to their healthcare team about management of their disease in light of the new therapies that we see all the time now, what advice would you give the patient? It's not a first meeting, but they're learning things for themselves and they're going back to their physicians for more information.
- Dr. Hellman: I think I would probably ask them to say to the healthcare team, "Teach me everything you can and don't assume that just because I've learned it, I haven't forgotten it, because most of this disease is going to be done by me. You need to help me and be there

when I am not as good as I could be, and if you accept that, I'll accept your imperfections too."

Jenny: What new drugs or technologies would be most helpful for type 1 versus type 2 patients?

Dr. Hellman: My experience has been that the fundamentals are not well understood, and I'll just comment briefly on that. In 1997 we published our outcomes study. Two years later we published our error data, and we were the first ones to show how much mistakes – whether it be from patients, nurses, doctors, or anyone else in the system – take away the outcomes. And it's not been really widely discussed except probably by myself – I'm a little nutty on that, I'm a little over the top on that – but my concern is people often take too much for granted. And yes, I absolutely love – we just finished a research study on one of the newer sensors – and we've been doing that for a while and in our practice we've worked with implantable pumps for 17 years. We've done a lot of things with some of the newer technologies, and my experience has been that there's so much that can be done by just having people learn the basics. Even the technology of glucose sensing, which I think will one day revolutionize the field of care, is probably not as central as some of the fundamental understandings that people don't yet have.

John: A final question: during your tenure as president, are we going to see AACE come out with a 6.0% A1c target, would you think?

Dr. Hellman: ...I think we need to balance and fit it to the needs of the particular patient. In general, the lower you can safely get it to be, the better off you are.

—by John Close and Jenny Jin

### 6. Conference Report

• Diabetes UK, March 14-16, Glasgow, Scotland, <a href="http://www.diabetes.org.uk/">http://www.diabetes.org.uk/</a>

At Diabetes UK, we saw excitement for incretin mimetics – new liraglutide data showing uniform drops in FPG and PPG, compared to Byetta's lower effect on FPG, and the good news that Byetta will be reimbursed for a year in the UK. Also, there was a call to pharmacotherapeutic action on obesity, since maintaining lifestyle usually does not work – what drugs to use remains a question, however, since there was negativity TZDs and it's unclear what rimonabant uptake has been like.

**New liraglutide data from Dr. Tina Vilsbøll**. Dr. Vilsbøll presented data from a 14-week trial with liraglutide that demonstrated 1.4% drop in A1c (1.7% from placebo, but there was a washout period before the trial began so we don't put much stock in this number). Notably, there were uniform drops in both fasting and postprandial glucose, in contrast to exenatide's lower effect on fasting glucose, so we would expect that the A1c drop would be bigger than what is seen with exenatide. The weight loss was 1.2 kg from placebo or 3.0 kg from baseline, and nausea was characterized as a "low risk." Interestingly, systolic blood pressure fell by 8 mm Hg, an effect that Dr. Vilsbøll said was beyond that of weight loss, and there were 20% reductions in other CVD risk factors like hs-CRP and PAI-1. The biggest finding was that liraglutide roughly doubled the acute first phase insulin response to IV glucose and the total insulin secretory capacity after 14 weeks of administration – though both were still lower than in normal controls. While this finding gets us closer to the elusive question of whether incretins increase beta cell mass, we note that it would have been stronger if they had shown that this effect was sustained in post-study washout (they didn't do a post-study washout). While intuitively it may make sense to assume that insulin secretory capacity is a proxy for the beta cell mass, in practice it may be that incretins are simply increasing the insulin secretory ability of each beta cell individually.

**Excitement about the availability of exenatide.** Byetta is now shipping in the UK, a bit ahead of the May 1 planned launch, and reimbursement looks promising for the time being – the Byetta booth was certainly packed at Diabetes UK. At the conference, Dr. John Buse and Dr. Dan Drucker gave talks on GLP-1 receptor agonists and DPP-4 inhibitors, respectively, both with positive views. Dr. Drucker argued that the DPP-4 inhibitors have probably been unfairly criticized for efficacy – they work well in combo, even if they lag metformin as first-line therapy. Dr. Buse reviewed both exenatide and liraglutide data and noted anticipation for exenatide LAR.

Medtronic's Paradigmn 522 pump presented. Medtronic was showing the Paradigm 522 pump and its the new mini-Link, which began shipping in mid-March in the US and Europe. Pump use is still very low in England, set by NICE (government guidelines) not to exceed more than 2% of type 1 patients. As we understand it, the 2% figure was chosen rather randomly. It sounds like pumps in Europe are selling best in Germany but followed by the UK, and there will be new pump guidelines by NICE in 2008. The new transmitter is very stylish - it is white rather than black, about 1/3 the size of the last (rather large) transmitter, and notably, the insertion is very close to the sensor, rather than dangling at the end of a "wire" like before - it now is Bluetooth enabled. It looks much easier to insert and is definitely more attractive. As would be expected, Medtronic seemed very happy about the new indication for children and teens for the Paradigm Real-Time Continuous Monitor - this is terrific to have available to this segment, even if reimbursement is difficult to come by in both the US and elsewhere. As. Dr. Murphy noted in his presentation, there is also a study underway to look at CGMS in pregnant women, both type 1 and type 2. Both types spend a surprisingly high amount of time in hyper- and hypoglycemia even when they were wellcontrolled as measured by A1c.

**Obesity needs to be treated with pharmacotherapy**. There was general consensus that lifestyle modifications are great when they work, but for most people they are just not enough when it comes to dealing with the 'obesogenic' environment of modern life. At the same time, effective drugs remain lacking. Dr. John Wilding gave an excellent talk on the amazing effects of bariatric surgery, but we note that this procedure is simply not practical to implement on a society-wide scale – even if it were safe enough to do.

Trial updates (DREAM, ADOPT, PROactive) generally negative on TZDs. Dr. David Matthews criticized the self-fulfilling design of DREAM by pointing out that if you give a glucose-lowering drug, then obviously you're going to reduce diabetes, but this tells us nothing about any underlying change in pathology. Dr. Edwin Gale similarly criticized ADOPT's trial design, including the somewhat bizarre endpoint of FPG >180 mg/dL. He concluded that rosiglitazone should not be used in prediabetes. Dr. John Wilding gave the most positive talk of the three, concluding that PROactive showed that pioglitazone may benefit people with a prior history of stroke or MI, and that the edema seen with TZDs can be managed and doesn't necessarily equate to heart failure. All in all, these three talks definitely made the case for TZDs in late disease but not in early disease.

Rimonabant is efficacious but safety questions remain. Nothing new here – Dr. Julio Rosenstock discussed the drug in two talks, reviewing results from SERENADE in one. We note that the higher rates of depression remain a concern, though the efficacy for both weight and A1c lowering looks good. Dr. Nick Finer also reviewed the mechanism of action for this drug. It was unclear what the uptake has been so far in Europe – it has had some reimbursement successes but by no means across the board – still we are impressed that the right patients are being targeted.

The genetics of diabetes and obesity are complicated, but candidate genes are emerging. Monogenic mutations (single mutations) that cause obesity are rare, accounting for only 7% of cases. For everyone else, a combination of genes and environment contribute. The TCF7L2 gene is the one most closely associated with type 2 diabetes, followed by the FTO gene, which contributes to type 2 diabetes solely by increasing the risk of obesity. Research on type 1 diabetes also yields interesting genetic implications: Infancy-onset insulindependent diabetes (IOIDD, or neonatal diabetes) is often associated with mutations to the Kir6.2/SUR1 membrane channel, which regulates insulin release, and children with this subtype of diabetes are often misdiagnosed as type 1, but would benefit more from sulfonylureas than insulin. Overall, type 1 remains difficult to understand – Dr. Edwin Gale thinks there's something causing people to get type 1 earlier rather than causing more type 1 overall, and this is the reason for the increase in recent decades.

• ADA Research Symposium: Translating Islet Biology into Diabetes Therapy, March 14-17, Stone Mountain, GA, www.diabetes.org/beta07

Below we present our highlights from the 2007 ADA Research Symposium on Islet Biology, sponsored by Eli Lilly and Amylin Pharmaceuticals. Attendees, primarily academic researchers (both MD's and PhD's), numbered just over 100. There were also many industry reps present – we talked with liaisons from Novartis, Amylin, Takeda, Merck, Pfizer, Novo Nordisk, BD, Metabolex, Amgen, Reddy Pharmaceuticals, Boehringer Ingelheim, Sanwa Kagaku Kenkyusho, LifeScan (transplantation division), and more. In general, attendees fell into two main groups: those who did basic research on beta-cells and (in some cases) knew very little about incretins, and those whose interest in beta-cell dysfunction has been provoked by the mechanism of action of the incretins. The audience seemed to perk up every time incretins were mentioned, and particularly when the question of how to measure the long-term effects of incretins on beta-cell mass was raised.

Type 2 diabetes is a dual defect disease (insulin resistance and beta-cell dysfunction). The bias at this conference was on the importance of beta-cell dysfunction in the pathology of type 2 diabetes, but our overall takeaway is that both defects are critical. Dr. Steven Kahn presented an extremely lucid view of the etiology of diabetes, noting that even for those with an environmental and genetic predisposition for obesity and insulin resistance, most people do not develop type 2 diabetes because their beta-cells compensate for decreased insulin sensitivity with increased insulin secretion. Only in a proportion of the population do the beta-cells fail to compensate – and then IGT/IFG and type 2 diabetes occur. This certainly explains the increasing prevalence of diabetes nicely: without obesity and insulin resistance, few people have poor enough beta-cell function to get diabetes, but with them, the genetic differences in beta-cell predisposition become clear.

Loss of both insulin sensitivity and the incretin effect occur early in disease. Dr. Jens Holst pointed out that once someone's fasting glucose rises above 6 mM, their incretin response is essentially gone. Dr. Kahn made a similar observation that insulin sensitivity begins to decline even in people with FPG between 80 and 90 mg/dL. This is important because insulin sensitivity seems to be the best predictor of incretin response. In diabetes patients, GIP secretion is normal but GIP response is lost, while GLP-1 secretion is lost and GLP-1 response is impaired but not lost. The latter is why GLP-1 replacement helps restore beta-cell function, but GIP does not.

On diabetes prevention: Euglycemia restores incretin sensitivity over time, which is why the DPP-4 inhibitors take about four months to show full efficacy, as patients become more sensitive to endogenous levels of GLP-1. Similarly, increasing insulin sensitivity with a TZD and thus reducing insulin demand is akin to diabetes prevention – both Dr. Kahn and Dr.

Robert Ratner equated beta-cell rest with diabetes prevention and noted that the degree to which a patient benefits from TZDs is highly dependent upon the degree to which restored insulin sensitivity reduces their beta-cell workload. To us, an interesting logical leap from the two observations that 1) insulin sensitivity is related to the incretin effect and 2) restoring insulin sensitivity helps prevent diabetes, is that perhaps restoring the incretin effect would prevent diabetes as well. Of course, two major problems with this hypothesis are the fact that loss of the incretin effect is secondary to diabetes, not a cause (as Jens Dr. Holst pointed out), and the fact that the TZDs delay diabetes by reducing beta-cell workload, whereas the incretins improve beta-cell function – which actually means increasing insulin secretion. Only a large-scale DREAM-like trial will tell.

**Beta-cell function does not equal beta-cell mass**. This idea goes hand-in-hand with the concept that beta-cell preservation does not equal beta-cell regeneration. Beta-cell function describes beta-cells' ability to secrete insulin in response to glucose, while beta-cell mass describes the actual number of insulin-secreting cells in the pancreas. The easiest way to think about the problem is to realize that loss of first-phase insulin secretion is not well correlated with loss of beta-cell mass. Dr. Juris Meier estimated there is ~80% loss of first-phase insulin response but only ~65% loss of beta-cell mass in people with long-standing type 2 diabetes. We assume that at least some of the missing insulin response is due to loss of the incretin effect, but even in obese individuals with normal glucose tolerance, beta-cell mass does not correlate well with function. Obese individuals have ~30% more beta-cell mass but ~200% more insulin secretion, which means that their beta-cells are compensating exquisitely well to the demands of increased insulin resistance.

Measuring beta-cell mass is really hard to do. Dr. R Paul Robertson gave an excellent lecture on the difficulty of assessing beta-cell mass using metabolic measures. Namely, it's impossible to measure beta-cell function by looking at glucose-dependent insulin secretion in people with diabetes because, by definition, they have a defect in glucose-dependent insulin secretion. Dr. Robertson suggested measuring the insulin response to arginine as a better proxy for beta-cell function. His talk was followed by three speakers on imaging techniques for measuring beta-cell mass: Dr. Alvin Powers' work on bioluminescence is useful in animals but not humans, whereas Dr. Paul Harris and Dr. Christopher McIntosh are working on ways to use PET imaging to measure beta-cells mass that may in time be applicable to humans – but the general consensus seemed to be that the technology is still far away.

The incretins are great drugs, but evidence for beta-cell regeneration is wanting. In conversation, Dr. James Foley of Novartis pointed out to us that even after one year of treatment with vildagliptin, once patients are taken off the drug they stop showing benefit. This suggests to him that there is probably no long-term effect on beta-cell regeneration. Dr. David D'Alessio said much the same thing in his presentation, noting that he isn't optimistic, but only an ADOPT-like trial will tell. Dr. Jens Holst told us that GLP-1 is undoubtedly a trophic factor – it definitely increases beta-cell mass – but only acutely, and beta-cell mass isn't a great measure of function anyway, so he's not sure about the significance. We were somewhat surprised by the general pessimism, but from what we heard, the data to date don't suggest a cure-like effect (which would be the natural outcome of actually restoring beta-cell mass), only good durability. On the other hand, at least one audience member suggested that with long-term studies with incretins, we would at best expect only a 10-20% increase in beta-cell mass per year, which may be why nothing measurable has been seen yet. Again, only time will tell. But, as Dr. D'Alessio pointed out, it's almost a moot point what the actual mechanism is: if the DPP-4 inhibitors, for example, show better durability than TZDs in an ADOPT-like trial, that will make them more attractive to clinicians.

**Beta-cells do regenerate... so is apoptosis the real problem?** There is ample evidence that beta-cells replicate in response to stress – the best example being the increase in beta-cell mass that occurs in people with insulin resistance and normal glucose tolerance. Dr. Susan Bonner-Weir gave a suggestive talk on the role of islet neogenesis (formation of new islets from ductal cells) in response to stress, though this is more controversial. Dr. Meier presented surprising research suggesting that even people with long-standing type 1 diabetes have a few beta-cells. He believes these cells come from islet neogenesis, but are being continuously destroyed by autoimmune processes. In type 2 diabetes, beta-cell apoptosis may instead be mediated through ER stress or mitochondrial dysfunction.

Mitochondrial dysfunction and ER stress are hot topics in beta-cell apoptosis. Dr. Marc Prentki and Dr. Orian Shirihai each gave talks on the potential role of mitochondrial dysfunction in mediating beta-cell death. Dr. Peter Arvan posited that increased insulin demand leads to ER stress, causing beta-cell death, while Jean-Christophe Jonas and Dr. Fumihiki Urano each pointed out that while physiological activation of the ER stress response pathway is actually quite helpful in increasing insulin secretion, chronic ER stress can eventually overwhelm the ER stress response pathway and lead to activation of apoptotic pathways. Various researchers are working on drugs that target the ER stress pathway for treating type 2 diabetes.

## American College of Cardiology, March 24-27, New Orleans, LA, <a href="http://acc07.acc.org/">http://acc07.acc.org/</a>

One of the largest medical meetings of the year, the American College of Cardiology's annual conference took place in New Orleans; we were glad the association helped support the city's revival. The conference covered all areas of cardiology, but we went to learn more about how cardiologists perceive and manage obesity, type 2 diabetes, and the metabolic syndrome. One New Orleans cardiologist told us, "Well, diabetes really is the driving force of this meeting." That was really something to hear.

We found a number of interesting differences between the attendees here and those at diabetes meetings. For both, weight loss is paramount, but cardiologists spend half (or possibly more!) of their time discussing diet and exercise, while endos and educators are, depending on your view, either more realistic or more jaded and don't seem to think as hard about how to achieve weight loss solely the old fashioned way.

We also noticed a far heavier bias toward oral drugs for diabetes at this meeting — cardiologists do certainly shy away from insulin and seem to put GLP-1 in the same bucket because it is injected (the education on this was minimal). Surprisingly, while in endocrinology, TZDs are taking the heat big-time right now for weight gain, edema, heart failure, and fractures, there was little criticism of the class at ACC. Prevention was discussed in terms of traditional cardiovascular agents. One doctor plaintively pointed out to us that diabetes is a vascular disease rather than a metabolic one. See below for our highlights.

Visceral fat and cytokines were hot topics, both in sessions and at Sanofi's booth, which was extravagant. The notion that visceral fat is what really matters is gaining steam and more widely discussed of late by thought leaders as well as Sanofi. There was a lot of excitement for Sanofi's rimonabant and notably not nearly the safety concerns we have seen from endos. Cardiologists want a good weight-loss drug that selectively reduces intra-abdominal adiposity (IAA) or visceral fat, and it is hoped that rimonabant may do this. Sanofi did not officially pre-market rimonabant, though its booth was packed (the video and laser pointer gift really helped, in our view). The reps were being very careful not to utter the word rimonabant, though - likely more so since the June FDA panel meeting has been announced. Some speakers suggested that the depression with rimonabant may be an indirect effect of losing intra-abdominal fat and not a direct effect of the drug. Dr. Jean-Pierre Despres, of Laval

University in Quebec, said that he's noticed that depression is a side effect of losing a lot of visceral fat – counterintuitively, since patients are losing weight! He said that this makes sense, given the way visceral fat is related to mood. Criticism of rimonabant was explicit in only one instance we saw, and even then, not so explicit. Dr. Elizabeth Barrett-Connor said her first premise for an anti-obesity pill is that it should be as good as diet and exercise. We respectfully disagree on this point because we think there are many patients who would not take part in diet and exercise, so for us that's too high a bar – a pill that simply encourages diet and exercise can be very helpful.

There was a huge Januvia push on the exhibit floor, but incretins were almost nowhere to be heard in the sessions. We were impressed with Merck's aggressive marketing here, as elsewhere, especially since incretins were not a hot topic at this meeting. There was no word on Janumet, which has now received approval – we would think cardiologists would also like the idea of combo therapy. Actually, Januvia's exhibit hall presence was really huge compared to how much it actually came up as a topic in sessions – very little. Merck was serving cappuccino, always a draw, but no naughty snacks this time. Amylin had no booth and Byetta had no presence, which we found surprising considering everyone was looking for weight loss, even in a diabetes drug. However, injections don't seem to be particularly accepted among cardiologists, even in cases where insulin or something strong is clearly warranted. Like Januvia, Byetta was virtually absent from sessions. Dr. Robert Eckel mentioned "fairly dramatic" weight loss in about a third of his patients on Byetta, but otherwise we found awareness of Byetta was scattered at best.

There was surprisingly little negativity toward TZDs, if any. They are not seen as wonder drugs, but their mild beneficial effect on cardiovascular intermediates seems to win cardiologists over. There was no talk of the side effects that the diabetes community has been buzzing more about since DREAM – notably, heart failure and fractures. Surprisingly, the weight gain was also just not discussed as a big issue. Overall, TZDs seemed to be a class of diabetes drugs that these doctors were most comfortable with. On the other hand, there was no particular enthusiasm for the class either, just a notable lack of aversion. Neither the GSK nor Takeda booths were especially well trafficked. Dr. Despres represented the uninspired, but not at all negative, attitude toward TZDs. At one point, Dr. Despres said that metformin doesn't affect visceral fat. TZDs, however, change the adipose tissue phenotype, which is "fine, but you have to explain to patients that you gain a lot of subcutaneous fat." On the other hand, with all the talk of CB1 receptors and increasing adiponectin, it was also mentioned that TZDs are pharmacologic activators of adiponectin secretion, which we found fascinating.

We sensed that cardiologists were all about orals, and compared to diabetes meetings, there was also a lot more talk on what the best diet is and what the best kind of exercise is. It was more idealistic than the discussions about patient adherence and adjunctive drug therapy that dominates lifestyle discussion at diabetes meetings. In general, the optimal treatment paradigm advocated by cardiologists often seemed like a cocktail of pills – a statin, a lipid-lowering drug, metformin or a TZD, and an ACE-inhibitor, or other combinations like that. We think this is probably also especially true for the internists, who have to treat the diabetes and the cardiovascular risk factors all at once. Insulin injections, for cardiologists, are complex. To us, Byetta seems far less complex (no dosing titration, weight loss, better A1c), but given the absence of any discussion of Byetta, we assume the cardiologists are not receiving much education on the drug.

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

#### 7. In the News

- The big are getting bigger the highest weight class is growing fastest: Reuters reported on April 9 that the severely obese are the fastest growing weight group in the US. In fact, however you cut it, the larger the weight class, the faster it seems to be growing. Based on self-reported data (which underestimates weight and therefore BMI), those with BMI of 30 ("obese") or more increased by 24% from 2000 to 2005; those with BMI of 40 or more ("severely obese") increased by 50% in the same time period; and those with BMI of 50 or more increased by 75%. Currently, obese Americans (those with a BMI of 30 or over) make up about 30% of the population, with the severely obese (those with a BMI of 40 or over) making up about 3%. Bariatric surgical procedures, which have risen a disproportionate 15fold over the last seven years, don't seem to be making a noticeable dent, though there is no control situation to compare it to. A surgeon at the Diabetes Technology Society in San Diego last week discussed the extremely poor durability of diet and drugs for obesity compared to surgery – drugs have a 95% failure rate in the severely obese and diets have a 95% failure rate in the overweight. Nevertheless, the data reported are evidence that the already large market for obesity treatments is still expanding. The full report will be published later this year in the journal *Public Health*.
- Speaking to the president of the AHA about encouraging Americans to "beat their risk:" During this year's Super Bowl, a commercial for the American Heart Association's online risk calculator caught Americans in the act of stuffing their faces with corn chips. The commercial involved a man in a red heart costume getting attacked by a gang of risk factors criminals labeled with "high blood pressure," "diabetes," "overweight," and "high cholesterol" (see the commercial at <a href="www.youtube.com/watch?v=Kgc-8KTMtl8">www.youtube.com/watch?v=Kgc-8KTMtl8</a>). Compared to a normal Sunday night, traffic to the website <a href="www.beatyourrrisk.com">www.beatyourrrisk.com</a> rose three-fold, and nearly 90,000 people visited the site in the weeks following. A preliminary analysis showed that three of four visitors are at higher than normal risk for a cardiovascular event. A Medical Broadcasting Company survey showed that the Internet is a health management tool for two out of three people, who research conditions before and after doctor visits online. The Internet is a great way to reach people with limited access or awareness.

—by Daniel A. Belkin and Kelly L. Close

### 8. Reviewing the Diabetes Literature

This month we include three short lit reviews of editorials and commentaries that caught our eye. First are two quick summaries two papers by Dr. Daniel Drucker and Dr. Louis Monnier on incretins in the March issue of *Nature Clinical Practice: Endocrinology and Metabolism*. This is followed by a summary of a series of letters published in the April issue of *Diabetes Care*, which debated various points from the ADA/EASD consensus algorithm for type 2 diabetes.

Main takeaways: 1) Dr. Monnier writes a scathing assessment of Dr. Steve Edelman's 2006 study of pramlintide as adjunct therapy to insulin in type 1 diabetes patients. He concludes that "there are no evidence-based data to justify the clinical use of pramlintide (at either fixed or progressive doses) as an adjunct to insulin therapy in type 1 diabetes." We were really surprised that he was so negative, given that he has done so much important work on glycemic variability his word carries a lot of weight. Granted, this isn't JAMA or Diabetes Care, but investors may still raise this - the good news is that this isn't the strongest paper from him (actually, it seems more like a rant, which struck us as very odd). See below for his criticisms and our take. 2) Dr. Drucker's editorial is essentially a call to endocrinologists to pay more attention to gut hormones, because they are very important in energy and metabolic homeostasis. This is a positive piece and reflects, we believe, the general consensus among endos that incretins will become an increasingly more important part of care in future years. 3) The April Diabetes Care

**letters showcased a "profound disagreement" between ACE/AACE and ADA/EASD regarding several major topics in diabetes treatment**. In their letter, ACE/AACE authors (Drs. Paul Jellinger, Harold Lebovitz, and Jaime Davidson) state that they believe newer therapies should have been included in the ADA/EASD type 2 diabetes algorithm because they have "new and unique" benefits. Dr. Mayer Davidson and Dr. David Nathan, on behalf of the ADA/EASD Consensus Group, say they disagree because of the lack of long-term safety data and high efficacy for these therapies. The ACE/AACE authors also believe that glycemic goals should have been set lower (they advocate <6.5% vs. the ADA target of <7.0%) and that postprandial glucose control should have been included as a goal. Drs. Davidson and Nathan again disagree because of a lack of strong clinical trials evidence that either would reduce long-term complications in type 2 diabetes patients. We found this to be a fascinating exchange.

- Monnier L. "Is pramlintide a safe and effective adjunct therapy for patients with type 1 diabetes?" Nature Clin Prac Endo Metab. March 2007. 3:332-333.
  - Dr. Louis Monnier of Lapeyronie Hospital in Montpellier, France, wrote a Practice Point on pramlintide in the March 2007 issue of *Nature Clinical Practice Endo/Metab*. Extremely negative, this short article first reviews the results of Dr. Steve Edelman's 2006 study (*Int J Clin Pract* 60:1647-1653), which looked at pramlintide vs. placebo as adjunct therapy to insulin in 295 type 1 insulin-treated patients over the course of 29 weeks, and then offers Dr. Monnier's commentary on the results of the trial.
  - **Dr. Monnier expresses disappointment with the results of the pramlintide study**. He notes that while the trial confirmed pramlintide improves postprandial glucose excursions for type 1 patients on basal-bolus insulin, he was "profoundly disappointed" by the finding that A1c levels did not improve for the pramlintide patients compared to placebo. He also criticizes the "absence of data on two of the main markers of diabetic control" in this trial: fasting plasma glucose and glucose variations; he cites his own work in noting that the latter is a potential risk factor for vascular complications. While we agree that glycemic variability was not explicitly measured in this trial, we would assume that reducing postprandial excursions would improve glycemic variability, since postprandial hyperglycemia is a major contributor to variability and because so often postprandial hyperglycemia results in hypoglycemia and resulting swings up and down just what Dr. Monnier says is so dangerous in his rodent work.
  - **Dr. Monnier goes on to question the reduction in insulin dose and weight seen with pramlintide**. He notes that the reduction in insulin dose was only 12% and the weight loss was only 1.3 kg. Considering that insulin causes weight gain, he suggests that the weight loss could have been due purely to reduction in insulin. We point out that numerous trials have shown that pramlintide does produce weight loss, and we don't think mechanism for weight loss really matters to patients while weight loss may not have been great in this particular trial (for whatever reason), most clinicians seem to be convinced that Symlin causes weight loss in most patients. In the trials noted on Symlin's label, we note that average weight loss was about 9 pounds for both type 1 and type 2 patients.
  - **Dr. Monnier notes that safety and tolerability also represent negatives to pramlintide.** The number of severe hypo episodes was higher with pramlintide in this trial, and we definitely see this as a negative but not to the extent that it should not be taken education and patient attention are key. Also, the incidence of severe vomiting was four times higher for pramlintide even with the progressive-dose escalation regimen, which leads him to reject the authors' claim that the dose escalation regimen improved tolerability. We note that nausea and vomiting are known side effects of pramlintide, and while we suspect they must prevent

some patients from going on (or staying on) the drug, in the clinical trials they seemed to decline over time with continued use.

**Dr. Monnier concludes that "there are no evidence-based data to justify the clinical use of pramlintide (at either fixed or progressive doses) as an adjunct to insulin therapy in type 1 diabetes."** He explains that the Edelman trial results were too mixed to justify a recommendation for pramlintide use. The only benefit was a reduction in postprandial glucose, which he does not consider sufficiently positive in light of the negatives: progressive dose escalation did not reduce the increased incidence of vomiting with pramlintide, A1c did not improve, and hypoglycemia was not reduced. We are very surprised that someone that argues against A1c-centricity doesn't see positives with reduced glycemic variability. He questions whether quality of life could have improved when the GI side effects were higher for treated patients, which makes us wonder how many patients he sees or how many patients he has spoken to who are on the drug. The anecdotes we've heard from clinicians with patients on Symlin suggest that while the drug is initially difficult to take, many patients who take it see a real benefit. This analysis does reinforce to us, however, that starting Symlin therapy can be difficult initially, that not everyone on insulin will respond to Symlin, and that some of the drug's benefits are non-obvious.

• Drucker DJ. "Unraveling the complexities of gut endocrinology." Nature Clin Prac Endo Metab. March 2007, 3:317.

Dr. Dan Drucker of the University of Toronto wrote the lead editorial in the March 2007 issue of *Nature Clinical Practice Endo/Metab*. In this editorial he urges endocrinologists to think about the importance of the enteroendocrine (gut hormone) system in metabolic and glucose homeostasis. In support of this point, he cites several examples of how genetic disruptions to the enteroendocrine system cause metabolic problems in humans:

- O Gut hormones are important for normal functioning: Children with mutations in neurogenin 3, a transcription factor necessary of development of pancreatic and gut endocrine cells, have severe diarrhea, metabolic acidosis, and nutrient malabsorption because they do not produce gut hormones.
- GLP-1 is important for normal functioning: Human with mutations in neuroendocrine convertase 1 (NEC1, formerly PC1) have small-bowel absorptive dysfunctions because NEC1 is required for the activity of gut peptides such as GLP-
- o TCF7L2 mutations may be linked to loss of GLP-1: Mutations to the TCF7L2 gene (which encodes transcription factor 7-like 2) are associated with type 2 diabetes in fact, this is currently the strongest genetic link to type 2 diabetes that we're aware of. Dr. Drucker points out that TCF7L2 is highly expressed in the gut, including the L cells responsible for GLP-1 production, which suggests that impaired TCF7L2 may be linked to defective GLP-1 production and/or impaired b-cell function.

Dr. Drucker concludes that with gut hormone treatments for obesity or diabetes receiving increased interest, the enteroendocrine system is becoming re-established as an important physiological system for regulating nutrient intake, absorption, and metabolic homeostasis.

• Jellinger PS, Lebovitz HE, Davidson JA on behalf of the ACE/AACE Outpatient Glycemic Control Implementation Task Force. "Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A Consensus Statement From the ADA and the EASD: Response to Nathan et al." Diabetes Care April 2007. 30:e16-e17.

Davidson MB. "Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A Consensus Statement From the ADA and the EASD: Response to Jellinger, Lebovitz, and Davidson." Diabetes Care April 2007. 30:e18-e20.

Nathan DM for the ADA and the EASD Consensus Group. "Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A Consensus Statement From the ADA and the EASD: Response to Jellinger, Lebovitz, and Davidson." Diabetes Care April 2007. 30:e21-e22.

Three heated letters were published in the April 2007 issue of *Diabetes Care* regarding the ADA/EASD consensus treatment algorithm for type 2 diabetes (published in *Diabetes Care* in August 2006). These letters detail what Dr. Nathan in his letter describes as "a profound disagreement between the AACE and the [ADA/EASD] consensus group" regarding the use of newer therapies for diabetes control as well as where A1c targets should be set and whether postprandial glucose control matters.

Who wrote the letters? The first letter, from Drs. Paul Jellinger, Harold Lebovitz, and Jaime Davidson on behalf of the ACE/AACE Outpatient Glycemic Control Implementation Task Force, criticizes many aspects of the ADA/EASD consensus algorithm – primarily the choice to exclude newer therapies as well as the setting of what they perceive as inadequate glycemic goals. The second letter, from Dr. Mayer Davidson, rebuts most of the points raised by the ACE/AACE authors. The third letter, from Dr. David Nathan on behalf of the ADA and EASD Consensus Group, provides further rebuttal to the ACE/AACE authors. While Dr. Davidson and Dr. Nathan's points largely overlap, there are a few small differences.

### Below we provide a summary of the five main points argued in these letters:

- The "philosophical problem" of rejecting newer therapies: Drs. Jellinger, Lebovitz, and Davidson note that "a philosophical problem [with the algorithm] is the rejection of the value of newer, well-proven treatments because they lack multivear clinical trials." That approach may deprive patients of "new and unique" agents for years. Dr. M. Davidson replies that the issue is one of safety, not efficacy, and notes that the Vioxx and Celebrex stories should be treated as cautionary tales. He argues that since the newer therapies are not more efficacious, they should not be recommended this early. While we agree that safety is very important, the evidence to date suggests that the newer therapies are actually more tolerable and possibly safer as well compared to older classes like the TZDs (weight gain, edema, congestive heart failure, and fractures!) and SFUs (weight gain). As well, the newer therapies may not be more efficacious, but they offer additional benefits like weight loss (i.e. exenatide), less variability (i.e. pramlintide), and ease of administration (i.e. sitagliptin) beyond those of traditional therapies. Dr. Nathan notes that, "the 'philosophical problem' ... represents a profound disagreement between the AACE and the consensus group." He says that based on the criteria the consensus group used to judge medications, there is simply not enough evidence to justify the inclusion of newer therapies at this time, though with new data the situation could certainly be changed.
- What criteria the ADA/EASD consensus authors were using: Drs. Jellinger, Lebovitz, and Davidson write that the authors of the algorithm were guided by "cost, evidence-based clinical trials, and experience with long-term use" when they drafted the consensus. Dr. Nathan writes that A1c lowering efficacy was actually the primary criterion the consensus group used to judge medications, but that secondary criteria also included "safety, side effects, tolerability and patient acceptance, other factors

that might reduce complications independent of glycemia, and cost." Dr. M. Davidson writes that cost was not a factor in the ADA/EASD consensus group's recommendation and points to the inclusion of the expensive TZD class as proof of this.

- O Whether the target A1c of <7.0% is too high: Drs. Jellinger, Lebovitz, and Davidson argue that the ACE and IDF-recommended target of <6.5% is supported by more evidence than the ADA target of <7.0%. They note that while the cost-effectiveness of this lower target has not yet been proven, it can be inferred from the likely reduction in complications. Dr. M. Davidson points out that numerous studies show that microvascular complications do not develop or progress at A1c <7.0%. Regarding macrovascular complications, he notes that studies among type 2 patients have been very mixed regarding the benefits of lowering glycemia so far all of the evidence for lowering glucose is epidemiological, not from randomized controlled trials, and thus only circumstantial. Dr. Nathan also writes as much, and adds that we should not recommend more intensive therapy until the results from ACCORD are published. We understand that hypoglycemia is a concern with intensified control, but note this is precisely why some people believe the newer glycemia-dependent therapies like incretins and DPP-4 inhibitors should have been in the algorithm.
- Whether postprandial glucose control is important: Drs. Jellinger, Lebovitz, and Davidson believe the omission of postprandial glucose control from the algorithm will make it difficult for patients to reach glycemic control, since postprandial glucose contributes more to A1c than fasting glucose at A1c <8.4%. They criticize the recommendation of metformin, which does not target postprandial glucose excursions, as first-line therapy and the exclusion of "exenatide, a-glucosidase inhibitors, rapid-acting insulin secretagogues, short-acting insulin analogues, and pramlintide," which do. Dr. M. Davidson again cites several studies on the significance of postprandial glucose excursions, with mixed results, and concludes that it is still "premature to recommend the specific targeting of postprandial glucose." However, he also notes that in early diabetes and in some patients under treatment, patients will have A1c >7.0% despite normal FPG because of elevated PPG, and in these patients treating postprandial glycemia is appropriate. We would think that this actually supports the idea of using glycemia-dependent drugs (like incretins, DPP-4 inhibitors, etc.) in early disease! Dr. Nathan calls "the enthusiasm of Jellinger, Lebovitz, and Davidson for the importance of postprandial glycemia" unsupported by data. He notes simply that clinical trial evidence is needed to prove that lowering postprandial glucose lowers A1c and complications.
- The heterogeneity of type 2 diabetes: The last matter that Drs. Jellinger, Lebovitz, and Davidson criticize is the algorithm's failure to address the fact that type 2 diabetes has different causes among different patients. In his reply, Dr. Nathan acknowledges this omission but explains that there are few studies that separate patients by phenotype or genotype, which is why no specific recommendations based on etiology are included in the recommendations. We think that this is a good future area for drug companies to focus on for example, the heterogeneity of weight loss with Byetta may be linked to the heterogeneous causes of either type 2 diabetes or obesity in patients taking the drug, so if we knew what the determining factors for efficacy were, then doctors would be able to predict which patients would be best to start on the drug.

—by Jenny J. Jin and Kelly L. Close

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