DIABETES CLOSE UP

Diabetes Close Up
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ADA Preview – Leading with Leptin

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

From the Editor:

We're headed to DC for the ADA *and so eager to see what the annual diabetes meeting has in store. As you will tell from the preview inside, we're excited about a range of posters and presentations and really are gearing up for an incredible five days. We will have our largest, most talented team at ADA and I'm so excited we'll be able to go to report on so much - Dan Belkin, Leah Edwards, Katelyn Gamson, Alyssa Gilbert, Cindy Glass, Jim Hirsch, Erin Kane, Patty Pringle, Alyssa Gilbert, and Cullen Taniguchi – and we feel so lucky to be going and covering it for you! Even with all of us going (albeit not everyone for five days), we barely feel we have enough bandwidth to cover all we'd like – that says a lot about the oh-so-dynamic state of diabetes today. It's getting even hotter and hotter…we're very geared up for a non-stop action packed five days and lots of compelling news and takeaways. We'll be sending out exclusive nightly updates to our subscribers via a nightly midnight blog as well as putting together a detailed ADA download for our July issue! In particular, we expect to hear lots about continuous monitoring, GLP-1, oxidative stress, inpatient insulin use, inhaled insulin, and DPP4 inhibitors – running through the abstracts, we were most impressed with items at the start of the list and we discuss this more inside in our ADA preview. Subscribers, if you haven't seen it and need some help figuring out what you'd like to look at this year – in addition to reading our story, you can download from our site an annotated ADA schedule and abstracts divided into major categories – this saves time sorting through 1600 or doing the dreaded copy and paste from the ADA website. We've got abstracts divided into glucose monitoring, continuous glucose monitoring, insulin pumps, insulin, inhaled insulin, GLP-1, DPP-4, obesity, oral abstracts, late-breakers).*

This issue is our most jam-packed ever in terms of access – we have interviews with endocrinologist extraordinaire Dr. Steve Edelman, noted food authority Marion Nestle, who is currently on her way across the country on a book tour for What to Eat (already a bestseller), and Rockefeller University scholar and Leptin authority (and inventor) Dr. Jeffrey Friedman. These are all very different conversations that we had and all truly remarkable in their own right. We are in awe of these two profound scholars and one brilliant, devoted doctor – we feel so lucky to be able to follow their work and to learn from them and we send enormous gratitude to them for sharing so much of their work with us, and with you. Enormous.

Our last topic is a bit political - the issue of competitive bidding around glucose monitoring is quietly becoming a hot topic, and this has us very concerned. Bottom line, we suddenly see a very *big risk that, as a result of the new proposed rules related to Competitive Bidding for Durable Medical Equipment, that Medicare recipients (easily a third of all patients with diabetes – 20% of people over 60 have diabetes, remember…) may soon only have access to the* least *expensive glucose meters and strips. What?!* I know. *This new program is scheduled to take effect in late 2007 in 10 of the largest major metropolitan areas in the US. If this happens, people on Medicare would be stuck with the cheapest strips, not the best ones, unless the final rules are modified. In order to ensure that Medicare can*

consider other (read: non-price) considerations in awarding bids for glucose testing supplies (this means, in order to ensure companies will still be able to invest in patient and provider education, innovation, customer service, etc.), we urge doctors and nurses, patients, concerned individuals, and anyone who cares about patients being able to monitor their diabetes optimally to submit comments in the open- comment period that ends on June 30, 2006. We are concerned that patients, out of nowhere, are going to be wind up with the short end of the stick because they will be stuck with meters and strips made by companies who don't invest in valuable innovation, education, and other services that are important to patients and health care professionals. Please *weigh in at the following website to register your thoughts: www.accessdata.fda.gov/scripts/oc/dockets/comments/commentsmain.cfm?EC_DOCUMENT_ID=100&SUBTYP=NEXT&CID=&AGENCY=CMS and let them know that patients want choice and need choice and will do far better* with *choice! And while you're at it, you might also let them know is that the problem is with lack of attention toward prevention and treatment, not the price of diabetes technology. We'll have a longer blog on how to make a difference here, and if you are interested in the details, please write me directly at kclose@closeconcerns.com. (BTW).*

'Til soon ~

-- Kelly L. Close

In this issue (see quotable quotes below):

1. **ADA Preview: Get ready, get set! Our top ten lists on what to see ….**
2. **Leptin: The Next Chapter (or, "Why Amylin is a Cheap Stock")**
3. **DCU Company Watch**
   - **Amylin – Dan Bradbury promoted**
   - **AstraZeneca – Analyst meeting update soon - dual PPAR finally dies**
   - **Medtronic – Gearing up to sell the 522/722**
   - **Dex Com – First revenues roll in**
   - **INGAP- Back to the Future**
   - **Conjuchem – Fundraising …**
4. **The First Amsterdam Diabetes Forum Review – A Focus on GLP-1**
5. **Pre-ADA, Hanging with Diabetes Guru Dr. Steve Edelman**
6. **Conference Report: AACE Highlights**
7. **Dining with the Author of *What To Eat*, Marion Nestle**
8. **Coming IPOs—HDI?**
9. **Literature Review: *Chest* journal – more hospital evidence by Krinsley**
10. **Upcoming Conference Preview**

Quotable Quotes – While it's a little unfair to share quotes without context, here are some of our favorites, from our interviews this month – read more, inside:

- **Dr. Marion Nestle:**
  - ***On advising in the real world****: "Again, my advice is simple: eat less, move more, eat plenty of fruits and vegetables and don't eat junk food. For somebody with diabetes, losing just a little weight will go a long way toward getting the blood sugar numbers under control. But the environment doesn't make it easy for any of us to do that. Right now, the default is to eat more, move less, and eat lots of junk food. We have to change that default."*
  - ***On making a difference:*** *"But every single time you order something in a restaurant or buy something in a supermarket, you're voting with your fork. You're making a statement about the kind of world you want to live in through the kind of food you want to buy."*

- **Dr. Jeffrey Friedman:**

- ***On the leptin discovery: "****So we embarked on what turned out to be an eight-year hunt for the gene. In 1994 we found it [leptin]. What we found was that the normal gene in OB mice is expressed primarily in fat tissue."*
- ***On the elegance of nature: "…****In a way, it solves this energy problem I told you about, if you think about it. Put it the following way: I'm not a religious person but it's the closest thing to a religious experience I've ever had. I don't believe in a god the way people do but I do believe in the mastery of nature and the beauty of nature and the natural world. It was sort of humbling, almost, to think of the problem that nature had to figure out, which is how to inventory all these calories and how beautiful the solution is. A lot of people who do research as I do, talk about how beautiful nature is and how beautiful science can be. This is for me my example. It is an aesthetically beautiful result when you understand the framework in which you think about it. …It's unbelievably elegant. So how does nature count calories? It makes a hormone that is a surrogate for the calories and the hormone conveys the aggregate number of calories that are stored and then reports that to the brain which makes adjustments."*

- **Dr. Steve Edelman:**
  - **On continuous monitoring and pumps**: *"I think the pumps (both disposable and traditional) will make it easier to act on the numbers people see on continuous monitors. I think everybody with type 1 could benefit from continuous sensing, whether they're on a pump or not. I'm not sure if that's going to drive more people to pumps, but I think people, regardless of whether they're on a pump, will benefit greatly from continuous monitoring …. Without a doubt, it definitely has the potential to revolutionalize management for type 1 patients. There's no question that most type 1s will do better having the DexCom STS or any other type of reliable continuous technology available 24 hours a day. It will reduce the standard deviation of blood sugars, reduce the wide fluctuations, protect against hypoglycemia, and it will allow type 1 patients to reach A1C levels that are closer to 6 percent much more safely. There just need to be reimbursement policies in place."*
  - **On Byetta**: *"Byetta is easy. I'm not surprised at all with the rapid uptake and growth of prescriptions - it's a blockbuster all the way, from start to finish. LAR will just make it even stronger. Primary care doctors are even using it a lot more than you'd expect, being a new injectable agent … Primary care is picking it up much faster than anybody would have predicted."*
  - **On Symlin**: *"Despite the uphill battles - you can't mix Symlin with insulin, you have to inject it, you have to deal with the rubber cement tops that dull needles, the potential for nausea, the need to titrate the insulin and Symlin… despite all that, the market share will grow. The vast majority of my patients who have started on Symlin have benefited from it tremendously. You must pick your patients wisely."*
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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 blog feed.

- **May 31: ADA abstracts – excitement abounds about Amylin!**
- **May 29: DPP-4 Smackdown!**
- **May 28: Killer Girl Scouts-on thin mints and trans fats**
- **May 19: New York Times' series highlights funding challenges for diabetes**
- **May 12: UCSF's Dr. German cites one-year time frame for islet from embryonic stem cell**
- **May 10: Critically ill patients live longer if obese?**
- **May 4: Beverage industry leaders agree to eliminate sweetened drinks from schools**
- **May 3: Morgan Stanley Unplugged – Pfizer's Exubera, delayed**
- **May 2: Hospitals offer obesity programs for children**

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

1. ADA Preview

American Diabetes Association 2006: Your Guide to Five Days, 15,000 HCPs, 63 symposia, 49 oral sessions, and 1600 posters

As we near publication, our ADA team is en route to Washington, D.C., where we will scour the exhibit hall, scribble notes in packed scientific sessions, and generally keep our ear to the ground at one of the two biggest global diabetes conferences of the year. Not only the biggest conference in the US, the 2006 ADA promises to be one of the biggest ADA meetings yet, and we're sent the largest ADA team in DCU history—10 in all, plus Kelly. Our post-ADA issue will be filled with our detailed notes on presentations and posters, from incretins to continuous monitoring and everything in between. After weeks spent in preparation for these critical days, we share with you here our tips on how to maximize your trip to ADA this year. For all the location particulars, download the schedule from our site, as well as the key abstracts!

If your passion is devices:

Five Sessions We Wouldn't Miss:

- Friday, 7:00 pm: Abbott-sponsored symposium: More Than We Imagined: CGM Raises Diabetes Management to a New Level
- Saturday, 5:30 am: Medtronic-sponsored symposium: Building a Foundation for the Artificial Pancreas: The Reality of Continuous Glucose Monitoring
- Monday, 2:15 pm: Reaching Out—Innovations in Technology
- Monday, 4:30 pm: Late-Breaking Clinical Trials
- Tuesday, 8:00 am: New Approaches to Glucose Sensing

Ten Must-See Posters:

- 1970-PO: OmniPod Insulin Management System: Patient Perceptions, Preference and Improved Glycemic Control HOWARD C. ZISSER, LOIS JOVANOVIC, PATTY SCHIFFLER
- 391-P: Accuracy of the Freestyle Navigator⊃® Continuous Glucose Monitoring System in Children with T1DM -- LARRY FOX, ROY BECK, STUART WEINZIMER, KATRINA RUEDY, CRAIG KOLLMAN, DONGYUAN XING, WILLIAM TAMBORLANE, DARRELL WILSON, PETER CHASE, MICHAEL TANSEY, THE DIABETES RESEARCH IN CHILDREN NETWORK, (DIRECNET) STUDY GROUP.
- 1811-P Changes in the Glycaemic Profiles of Women with Type 1 and Type 2 Diabetes Wearing Continuous Glucose Monitoring Systems (CGMS) for 7 Days at Monthly Intervals throughout Pregnancy -- HELEN R. MURPHY, DUNCAN FOWLER, GERRY RAYMAN, ROSEMARY C. TEMPLE.

- 1957-PO Diabetes Research in Children Network (DirecNet) Pilot Study To Evaluate the Freestyle Navigator Continuous Glucose Monitoring System in the Management of T1D in Children -- ROSANNA FIALLO-SCHARER, WILLIAM TAMBORLANE, BRUCE BUCKINGHAM, TIM WYSOCKI, STUART WEINZIMER, EVA TSALIKIAN, ROY BECK, KATRINA RUEDY, CRAIG KOLLMAN, THE DIABETES RESEARCH IN CHILDREN NETWORK, (DIRECNET) STUDY GROUP.

- 1-LB Reduction in A1c with Real-Time Continuous Glucose Monitoring: Interim Results from a 12-Week Clinical Study -- TIMOTHY BAILEY, ROY KAPLAN, SHERWYN SCHWARTZ

- 2-LB Performance of the FreeStyle Navigator Continuous Glucose Monitoring System during Home Use -- B. BODE, R. BERGENSTAL, R. WEINSTEIN, R. BERNSTEIN, S. SCHWARTZ, S. EL-DEIRY, J. BUGLER

- 71-OR Clinical Trial of a Seven-Day Continuous Glucose Sensor Demonstrates the Importance of Fasting Hyperglycemia and the Dawn Phenomenon -- SATISH K. GARG, LOIS JOVANOVIC.

- 393-P Improvement in Glucose Excursions Using a Seven-Day Continuous Glucose Sensor: Managing the Extremes -- SATISH K. GARG, HOWARD C. ZISSER, LOIS JOVANOVIC.

- 431-P Automated Feedback-Controlled Insulin Delivery in Children with Type 1 Diabetes Mellitus (T1D): A Preliminary Report -- STUART A. WEINZIMER, GARRY M. STEIL, NATALIE KURTZ, KARENA L. SWAN, WILLIAM V. TAMBORLANE.

On booths:

- The **DexCom** booth, which we previewed at AACE, is a must-see. DexCom's strike-while-the-iron-is-hot launch is in full force, and their enormous screen will be playing their "live life interrupted" video.

- We expect the **Medtronic** booth to be buzzing with the new 522/722

- The disposable pump by **Insulet**, though not available everywhere yet, has captured the interest of patients and HCPs alike, and we expect to see considerable interest at their booth.

- The Abbott booth will be a place to be, what with the excellent poster they've got – hear more at the booth.

If you're keeping an eye on drugs:

Ten Sessions We Wouldn't Miss

- Friday, 7:00 pm: Novartis-sponsored symposium: The Clinical Impact of Incretin-based Therapies on Type 2 Diabetes Management: One Year Later

- Saturday, 8:00 am: Leveraging the Clinical Potential of GLP-1: Two Perspectives

- Saturday, 10:15 am: Obesity Treatment—Behavioral versus Pharmacological versus Surgical Approaches

- Sunday, 8:00 am: GLP-1—The New Darling of Diabetes Treatment

- Sunday, 2:00 pm: Beta-Cell Regeneration—Moving to the Bedside

- Sunday, 2:00 pm: New Hormonal Targets for Diabetes and Obesity Treatment—The Good, the Bad, and the Ugly

- Sunday, 4:15 pm: PPARs and CVD

- Sunday, 6:00 pm: Pfizer-sponsored symposium: Debating the Management of Type 2 Diabetes with Emerging Therapies

- Monday, 5:30 am: Lilly/Amylin-sponsored symposium: A 2006 Update on Incretins in Type 2 Diabetes

- Tuesday, 8:00 am: Inhaled Insulin—Metabolic and Pulmonary Issues

Five Must-See Posters

- 116-OR Effects of Exenatide on Gastric Emptying and Postprandial Glucose in Type 2 Diabetes
  HELLE LINNEBJERG, SOOMIN PARK, PRAJAKTI KOTHARE, MICHAEL TRAUTMANN, KENNETH MACE, MARK FINEMAN, IAN WILDING, MICHAEL NAUCK, MICHAEL HOROWITZ.

- 118-OR Contribution of Glucagon Suppression to Improved Postprandial Hyperglycemia Induced by Exenatide in Patients with T2DM
  ESTELA WAJCBERG, CURTIS TRIPLITT, API SRIWIJITKAMOL, RALPH A. DEFRONZO, EUGENIO CERSOSIMO.

- 456-P Substituting Exenatide for Insulin in Patients with Type 2 Diabetes: An Exploratory Study
  STEPHEN DAVIS, DON JOHNS, DAVID MAGGS, JUSTIN NORTHRUP, HANGTAO XU, ROBERT BRODOWS

- 326-OR Equivalence of Basal Insulin Glargine vs Prandial Insulin Lispro for Glucose Control in Type 2 Diabetes Patients on Oral Agents – Results of the APOLLO Study
  REINHARD G. BRETZEL, THOMAS LINN, FOR THE APOLLO STUDY GROUP.

- 109-OR Inhaled Human Insulin (Exubera) Therapy Shows Sustained Efficacy and Is Well Tolerated over a 2-Year Period in Patients with Type 2 Diabetes (T2DM)
  JULIO ROSENSTOCK, HOWARD FOYT, SOL KLIOZE, MASAYO OGAWA, LISA ST AUBIN, WILLIAM DUGGAN.

On booths:

- Amylin, Amylin, Amylin, and more on Byetta and Symlin

- Now that Exubera has received approval, we expect the **Pfizer** booth to provide something in the way of information or a prototype of the Exubera inhaler. Though the launch has been a bit delayed, look for interest here.

- DPP4s – check out Novartis, Merck, and BMS

—By Erin Kane and Kelly Close

2. Leptin: The Next (Exciting) Chapter

PART 1: Introduction

DCU visited Dr. Jeffrey Friedman, the discoverer of leptin, in his office at Rockefeller University on a beautiful day in late April. We had been looking forward to this appointment, which we made soon after Amylin announced it was acquiring the rights to leptin from Amgen earlier this year. Dr. Friedman is a member of Amylin's Scientific Advisory Board, and our goal in meeting him was to find out more about the renewed prospects for a hormone that had created so much excitement in the biotech community back in the 1990's, only to disappoint expectations in clinical trials. And disappoint in a most frustrating way—leptin clearly played a critical role, or roles, in the maintenance of human metabolism and was likely an important part of the answer in controlling weight, but much more needed to be understood about how the body regulates weight and the complexity of likely redundant pathways.

Fortunately, even if the wheels of commerce grind to a halt, the science continues. According to the Howard Hughes Institute, more than 4,200 papers have been published on leptin since its discovery; PubMed lists more than 10,000. A few weeks ago, more than 10 years after Amgen paid $20mm upfront to license leptin from Rockefeller University (1995), and almost seven years since Amgen abandoned leptin as a potential stand-alone therapy for the treatment of obesity in the general population (1999), the World International Patent Organization published an Amylin patent that claims a combination of amylin (aka pramlintide or Symlin) and leptin for the treatment of obesity. The claim is for "a method of reducing body weight in a subject comprising administering at least one of a leptin, a leptin derivative or a leptin agonist and at least one of an amylin, an amylin agonist or an amylin analog in amounts effective *to reduce the body weight of the subject by at least 10%* (emphasis added)."

Any thoughts that this claim, in a very full patent submission, merely represented the thoroughness of intellectual property lawyers were dispelled when the list of late-breaking presentations at the ADA was published a few days ago. Significantly, these included a submission from Amylin entitled "Leptin Responsivity Restored in Leptin-Resistant Diet-Induced Obese (DIO) Rats: Synergistic Actions of Amylin and Leptin for Reduction in Body Weight (BW) and Fat," by a group of Amylin researchers that included two of our favorites, Dr. Christian Weyer and Dr. Alain Baron. From the on-line abstract (52-LB) we learned that leptin and amylin appear to operate synergistically, with weight loss over two weeks of 2.7% for leptin-treated DIO rats, loss of 6.7% for amylin-treated rats, and weight loss of 12.0% for those treated with a leptin/amylin combination. From the authors:

> In sum, amylin+leptin co-treatment: (1) reproducibly induced synergistic, sustained BW loss (2) specifically decreased adiposity while sparing lean mass, and, (3) exerted effects through multiple mechanisms partially dissociable from amylin's anorexigenic properties. These studies provided pre-clinical proof of concept for amylin *restoring leptin responsivity* in obesity, *a finding to be further substantiated in preclinical and clinical studies* (emphasis added).

We look forward to reporting in more detail about the clinical prospects for leptin in our post-ADA report. We might also get additional commentary from Dr. Friedman, although he has been properly circumspect in commenting on Amylin's program. In the meantime, we are publishing "Leptin 101", which will serve as a backgrounder for those either too young or forgetful to remember the reasons for the early excitement and, ESPECIALLY, why the promise of *restoring leptin responsivity* is so exciting.

PART 2: Leptin 101 - A Brief History

The history of leptin is inextricably tied to a strain of spontaneously obese mice from the Jackson

Laboratories called the ob/ob mouse. These mice suffer from extreme obesity due to a combination of hyperphagia (overeating) and decreased metabolism (decreased fatty acid oxidation in muscle and liver). These mice are nearly double the weight of normal mice, and all the weight is from fat. Put into perspective, a normal mouse is about the size of a large walnut, while the ob/ob mouse is about the size and shape of a tennis ball. Interestingly, these ob/ob mice also have many other problems including alterations of bone growth, immune alterations, infertility, and abnormally low thyroid function.

The first clue to the cause of the massive obesity in ob/ob mice was found by doing parabiosis experiments, where the blood supply of an ob/ob mouse was fused with that of a normal mouse (the mice are literally sewn together). Scientists found that parabiosis reduced the obesity of ob/ob mice, and deduced that the defect in these mice must come as a result of the lack of circulating factor present in normal mice. But exactly what this factor was and where it was secreted was a mystery.

The big break in the field came in 1994, when Dr. Jeffrey Friedman cloned the ob gene and found that it encoded an adipocyte-derived hormone he called leptin (which comes from the Greek word "leptos" meaning "lean"). In the following section, we excerpt some quotes from our recent conversation with Dr. Friedman on his role in discovering leptin and its possible uses for the treatment of obesity and diabetes in the future (full text of the interview at www.closeconcerns.com).

Although fat cells, or adipocytes, are often maligned as the storage depots of excess energy, it is now known that fat cells also secrete hormones that inform other tissues about the nutrient status of the body. Adipocytes secrete the hormone leptin from adipose tissue, which essentially informs the rest of the body about the state of fat (energy) stores. Changes in fat mass result in changes in plasma leptin level. Deviations in the levels of leptin elicit adaptive biologic responses designed to return fat levels to their start point that includes alterations in food intake, metabolism and many other physiologic systems. In a sense leptin is a key signal that connects changes in nutrition to compensatory changes in many (possibly all) other tissues. One major effect of leptin is to signal feeding centers of the brain to curb appetite.

While the efficacy of leptin to treat obesity in the general population has not been firmly established yet, a number of human conditions associated with leptin deficiency have been shown to be effectively treated with this hormone. Animals or humans lacking leptin are extremely obese and respond with a dramatically reduced food intake and body weight after receiving injections of the hormone. Leptin also has powerful effects in other tissues (Kahn and Flier, 2000). Most notably, it improves insulin sensitivity. For instance, leptin increases glucose uptake in muscle and suppresses hepatic glucose production in the liver. Leptin also enhances the burning of fat molecules in other tissues, most notably in the liver. These insulin sensitizing effects can be most dramatically seen in patients with a rare disorder called lipodystrophy, a condition associated with the congenital or acquired absence of fat tissue. While having very little fat may sound appealing initially, these patients are not very healthy and develop severe diabetes. Since lipodystrophic patients do not have fat, they cannot secrete leptin and thus are severely insulin resistant, since leptin normally sensitizes tissues to insulin. (Although lipodystrophic patients do not secrete leptin, they cannot become obese since they do not grow fat cells). Interestingly, leptin therapy completely reverses the insulin resistance of lipodystrophic patients and has been hailed as a major breakthrough in the treatment for this rare disorder (Petersen et al., 2002). Because of these very powerful effects on metabolism, leptin has been recognized as an important regulator of body weight, both because of its appetite-suppressing effects and its insulin sensitizing effects in the periphery.

In addition, leptin's actions are linked to other areas of the brain that control fertility: Mice and humans that have low leptin levels are infertile, because low leptin levels signal to the brain that the body requires more fuel. Teleologically, you could say that nature built in a system to ensure that reproduction could not occur unless there were sufficient energy stores to see a fetus through term. Interestingly, leptin will restore fertility in some infertile patients; it has also been used recently to treat patients with hypothalamic

amenorrhea (Schellekens, 2004).

The role of leptin in obesity and diabetes in humans is still not clear. As mentioned earlier, lipodystrophic or leptin-less patients are readily treated by recombinant leptin. These successes made the promise of leptin therapy for diabetes seem plausible; however, much to chagrin of scientists, most obese humans were found to already have high circulating levels of leptin. This unusual fact can be explained in part by the fact that leptin is known to be secreted in amounts proportional to the total amount of fat. Although one would expect that these elevated leptin levels in the blood would curb appetite and increase fat oxidation in the liver, this is often not the case. This phenomenon, called "leptin resistance," is now known to be common in obesity and is now being better studied at the molecular level. *Thus, part of the reason that leptin may have failed as a treatment in its early clinical trials was that many obese people were probably severely leptin resistant.*

Summary of leptin action

Tissue	**What leptin does**
Hypothalamus	Suppresses appetite, restores fertility
Liver	Suppresses hepatic glucose output, increases fatty acid oxidation
Muscle	Increases glucose uptake, increase fatty acid oxidation
Pancreas	May antagonize insulin release. This is controversial
Fat	Leptin is secreted by the fat, what causes leptin secretion is unknown

Conclusions

The modulation of feeding pathways and enhancing leptin sensitivity may represent a major paradigm shift in the targets of type 2 diabetes treatment. If Amylin can indeed restore leptin sensitivity in obese and diabetic patients, then leptin could finally be used effectively in a clinical setting to both improve insulin sensitivity and perhaps curb appetite. While it remains to be seen whether leptin can make a "comeback" as a therapeutic, we are indeed hoping that leptin can live up to its initial promise as potent treatment for the growing scourge of diabetes and obesity.

PART 3: Gems from Dr. Friedman

Dr. Friedman had many interesting thoughts in our 90- minute talk – we share some highlights below. To read the full story of leptin's discovery and Dr. Friedman's views on its applications, please visit the Close Concerns website.

On the discovery of leptin:

So we embarked on what turned out to be an eight-year hunt for the gene. In 1994 we found it. What we found was that the normal gene in OB mice is expressed primarily in fat tissue.

We had been working on it for quite some time. The way that the approach we used works is this: You try to identify a gene, not based on knowing in advance what it does but simply based on a detailed knowledge of its precise position on chromosome. So using standard genetic tools, you can narrow the search for the gene to a particular segment of the chromosome. I had reasoned in advance that we could use [these tools] to narrow the gene to about 500 kilobases, which would be in the mouse 1/6000th of the whole genome. So there are tools that allow you to narrow it to that point but, once there, you can't feasibly narrow it any further. So in a 500 kilobase interval, there would be, let's say, 5 to 10 genes.

What one does is to try to go about isolating each of them and then empirically asking: "Is this gene defective in the animal? Is this gene defective in the animal? Is this gene defective? Is that gene defective?"

The hard part about this project, in a way, was that you work all this time, you're not sure if you're ever going to find it. If you don't find it, was it because there was an error here or the methods weren't good enough? In addition, there is an element of chance because lots of genes were being cloned and it could happen by chance that someone would find a gene, learn that it mapped precisely to that region, and they would be able to find OB just because they stumbled onto it. So it was anxiety provoking.

There we were. We had the 500 KB interval. We're looking at genes. One day on a Friday, we get [the] data. I remember this because I just happened to be giving a lecture at the university this day, a big lecture. I closed my talk by saying, "And here's one of the genes in the interval. It is expressed primarily in fat." Well, I was not unaware of the possibility that that could be the OB gene and I think I said so at the end of the talk, but consciously, I couldn't even grasp the possibility that this might be it.

The next step is to ask: Is that gene altered in OB mice? So that weekend, we set out to do it. One of the people in the lab did a preliminary experiment that showed that one of the two available mutations in OB [Sm/Ckc ob/ob] doesn't make RNA for this particular gene. That used a PCR method. It was pretty exciting but there are ways to get false results with PCR so it was not definitive. The definitive result would be to do what's known as a Northern blot which allows you to look very precisely at RNA levels, both qualitatively and quantitatively.

So on that Saturday, which was May 7th, 1994, I frantically looked for a blot that someone else in the lab had made with the probe so I could set up the experiment. I couldn't find her. I set it up myself at like five in the afternoon. I came back at around 12:00 to wash it and put it under X-ray film, which is how you get the result. I couldn't sleep that night so I woke up at around 5:30 or 6:00 the next morning and I developed the film. I have the film up in my office there.

(pulls it down from the wall)

...This is RNA. This is before there were computers, you know, you didn't scan things in those days. You would take a photo of an experiment and then a big photo. You would cut and paste it and then this is the way you would make figures before computers...You see here, this is how the RNA gets detected. There is no RNA in the brain and all the rest are fat. So there is RNA in this animal but it's a normal animal. This is the mutant [Sm/Ckc ob/ob], no RNA.

This is the animal that had no RNA by PCR. This is the animal that Coleman worked with [C57BL ob/ob, "OB classic"], that's the one there is a picture of, RNA and fat. But now, the mutant [C57BL ob/ob] has a huge increase in RNA and that's why we saw it on PCR and couldn't figure out what was going on.

I looked at this at 5:30 in the morning and the second I looked at it, I knew that we had not only cloned the OB gene but that it was under feedback control, which was consistent with Coleman. Let me tell you why. It's easier to understand why this animal [Sm/Ckc ob/ob] is obese. It doesn't make the RNA. What about this one [C57BL ob/ob]? It over-produces it. Well, the idea here is maybe the RNA encodes a defective protein and the gene is under feedback control so no active protein is made and it secondarily over-produces it [the defective protein], [as with] the DB mutant.

On the elegance of nature: *In a way, it solves this energy problem I told you about, if you think about it. Put it the following way: I'm not a religious person but it's the closest thing to a religious experience I've ever had. I don't believe in a god the way people do but I do believe in the mastery of nature and the*

beauty of nature and the natural world. It was sort of humbling, almost, to think of the problem that nature had to figure out, which is how to inventory all these calories and how beautiful the solution is. A lot of people who do research as I do, talk about how beautiful nature is and how beautiful science can be. This is for me my example. It is an aesthetically beautiful result when you understand the framework in which you think about it.

...It's unbelievably elegant. So how does nature count calories? It makes a hormone that is a surrogate for the calories and the hormone conveys the aggregate number of calories that are stored and then reports that to the brain which makes adjustments.

On christening leptin:

The reason we picked the name leptin, or I picked the name leptin, is this: I'd gone years before to a meeting in Grenada. It was sort of a boondoggle and a group that was organized by the head of psychiatry at NYU. It brought different people together and one of the people – it was actually a very distinguished group. I was not so, I was much younger, but one of the people there was a guy named Roger Giaman, whom you might have heard of. He won the Nobel Prize for the hypothalamic releasing factors.

I gave this talk and got to know Roger. He was quite a charming fellow. Actually, one of the other people there was a guy named Arvid Carlssen, who went on to win the Nobel Prize a few years ago for dopamine. So anyway, I get a letter, a very polite letter, from Giaman months after, saying, "I really liked meeting you. I liked your talk. I do have one thing to quibble with you about. You referred to this as an obesity gene because everybody looks at the animal and says it's an obesity gene. But, he said, of course, the normal gene isn't an obesity gene. The normal gene keeps you thin and it's only when the gene is defective that you get fat. So I think you should no longer refer to these as obesity genes but leptogenes." He said, "I chose the root, lepto, from the Greek root meaning thin."

We proposed the name in this July 1995 paper and it was only with difficulty – they wouldn't let us call it leptin in the title but at the last paragraph, we just got to say we propose that this be called leptin because in its absence you're fat. There were three papers reporting bioactivity at the time…There were three papers that reported bioactivity and everyone was really excited. One of the other papers proposed the name "OB protein". I was really sort of put off by that and was worried that the world would refer to this as OB protein. I was glad that leptin stuck.

On how leptin may be used as a fertility treatment:

The second clinical entity for which leptin, I think, has some promise now is something called hypothalamic amenorrhea. This is long distance runner syndrome or ballet dancer syndrome. These are women who are extremely thin, who have very little adipose tissue and have low leptin levels and often stop menstruating. In addition, this condition is associated with other alterations of the neuroendocrine axis. There was a report in the New England Journal a year or two ago that leptin treatment of seven of these women restored reproductive function and corrected these other abnormalities.

I am told that this condition is more common than I had appreciated. I'm told by the person who published it – his name is Chris Mantzoros [of the Beth Israel Deaconess Hospital in Boston] – that 1 in 3 visits to an infertility clinic by a woman are accounted for by this and that 4% to 8% of women are affected. So there are potentials for leptin treatment of this condition or delayed puberty in girls who don't enter puberty normally because they are extremely thin. There is also some potential for treating these associated abnormalities which are under-appreciated in that subgroup such as bone loss. There is

very severe bone loss early that is not simply a consequence of the lack of estrogen. So that's another opportunity.

On how leptin may be useful in weight management:

The hard part for people who are obese, oftentimes, is not taking the weight off but keeping it off. It is now known that when weight is lost, leptin levels fall. The idea is that when you now have a leptin level lower than you're used to, that is a stimulus to eat more and is part of the drive to regain the lost weight. So the question is, if you lose weight by dieting and leptin levels fall, does replacing or restoring the leptin back to the starting point now keep you from regaining the weight? So one of the things that might get tested is that, either in the context of weight loss by dieting or post-gastric bypass. One of the things that might get tested is whether giving leptin back can maintain weight loss or prevent some of the other complications that develop.

On other therapeutic applications for leptin:

It turns out that part of the reason no one could figure out what was going on with the OB mice is that they have abnormalities in every physiologic system you looked at. There are 10,000 papers written about OB mice before the gene was cloned and no one could make sense of it because all of these features are not the sort of features you see generally in obese patients. It turned out that the leptin deficient children – and I'll show you a picture of these kids in a minute – manifest exactly the same set of alterations. They are insulin resistant. They don't enter puberty normally. They have immune dysfunction. They have other neurorendocrine problems, etc. It turns out leptin fixes all of these other abnormalities, not just the obesity, which is why this idea that low leptin is a signal for many changes came from. Well, there are other pathophysiologic states associated with low leptin levels besides leptin mutations of the sort that the kids have. Leptin has proven to be very effective in probably all of them. So let me give you a few examples.

There is a diabetic condition known as lipodystrophy. This is the loss of fat. It's sort of like the fat equivalent of muscular dystrophy. The fat disappears either because of an inherited defect or it can be acquired. Because the fat is gone, the leptin is gone. It turns out these people develop probably the most intractable insulin resistance you'll ever see, a huge fatty liver and a really life threatening condition in some cases. It has been shown now that leptin replacement of these individuals restores insulin sensitivity and treats the fatty liver. It is a pretty effective, well-accepted therapy now for lipodystrophy.

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—By Cullen Taniguchi, Alyssa Shell, and Kelly Close

3. DCU Company Watch

Amylin - Succession planning at its best! Amylin announced that the very talented Dan Bradbury would become President of Amylin, effective June 7, as well as CEO of Amylin, effective sometime over the next year. For the last three years, Dan and Ginger Graham, the commercialization whiz/guru who has overseen a most most productive time at Amylin since novel drugs Symlin and Byetta were approved last spring (2005), have had an extraordinarily effective COO-CEO partnership - we expect this to continue during succession transition time over the next year. Dan has been at Amylin for twelve years and has been long-regarded as the "get it done" guy behind some very talented visionaries: Ginger Graham and Joe Cook. Amylin couldn't be at a stronger point in its history and what better time for Dan to be promoted. We were lucky enough to see him present just a few weeks ago in Miami at Morgan Stanley's (fantastic) Unplugged conference and there couldn't have been someone more crisp, calm, cool, or collected. And just think about all that's yet to come ~ TZDs and Byetta, Byetta monotherapy, Symlin for obesity, Leptin combos, Bio-Nebraska, the new-in-man-this-year obesity compound, the other unnamed compound that moved into the clinic this year ...oh, and LAR. Onward!

AstraZeneca – Galida Bites the Dust: We'll be out with a blog on whatever AZ says on diabetes, which is happening as our issue goes to press at its annual investor meeting in London – Galida bit the dust officially last month, which was long-awaited as yet another dual PPAR died.

Medtronic—Gearing up …: Medtronic posted another quarter of disappointing diabetes revenue, as it was hurt by disposable-related billing problems. They are undoubtedly looking forward to marketing the newly-approved sensor-augmented pump – sensors will be available as of mid-June, though reimbursement likely won't emerge in our view until well into 2007. For the fourth quarter ending in April, Medtronic's revenue from diabetes' products was $189 million, up just five percent from last year's revenue of $179 million. For the fiscal year, diabetes revenue was $722 million, up 11 percent from year-ago revenues. This quarter marks Medtronic's second consecutive quarter of slow diabetes growth, with 6% growth last quarter. In comparison, the fiscal fourth quarter in 2005 showed a 24% growth in sales. Medtronic said its revenue for pump hardware increased by the "mid-teens" while its growth in disposables experienced a "slight decrease." Management blamed "excess customer oversupply" of disposables and billing problems for its drop off in disposables. We do know customers who say they have received too many disposables – we always keep in mind that although patients are encouraged to change sets every three days, this doesn't always happen, especially since many patients can make a set "last" four days or more. While billing matters are being resolved, Medtronic is benefiting from the fact that Insulet isn't rolling out faster (they want the time to be absolutely ready, from what it sounded like from CEO Duane DeSisto's recent talk at Morgan Stanley's Unplugged conference - since 80% of the patients moving to Omnipod are actually MDI - multiple daily injections - they aren't in a rush and why should they be! Smart to avoid rushing a product to a full launch, though due to word of mouth, patients are eager, even inpatient to try it...) but it may see a dent in sales if more Medtronic users decide to move to the OmniPod. No doubt the sensor augmented option will appeal to many users in theory, although until reimbursement emerges, we're not sure how many will take advantage. Continuous monitoring systems could help pump sales, but it has real competition with DexCom's tiny STS and Abbott's Navigator, which we would expect to emerge sometime this year. On a positive note, we believe that reimbursement will emerge and that a thriving market for sensors will eventually ensue – which in itself will drive pump sales. That news is excellent news for Medtronic, the market share leader in pump sales.

Medtronic management was enthusiastic about the approval of 522/722, (its sensor-augmented pump) calling it "the highlight of the quarter." The device allows 100 times more glucose readings than "three fingersticks a day." Feedback on the Guardian RT has also been very positive. The STAR trials, undertaken to support use and reimbursement for continuous glucose monitoring systems, are enrolling

subjects. The STAR 1 trial has completed enrollment and its results are expected to be available in the first half of the 2007 fiscal year.

Watch out for Medtronic at this year's ADA, where it's sponsoring a corporate symposium on Saturday morning, June 10th, titled "Building an Artificial Pancreas: The Reality of Continuous Glucose Monitoring." An analyst meeting and webcast is also planned for June 12th -

DexCom—First revenue rolls in: DexCom reported its first quarter results on May 16th. Company revenues totaled $15,000 and total losses were $10.9 million for the first quarter. DexCom raised $47 million recently through a secondary offering (timing perfect, right after STS approval)**,** increasing its cash to $67 million dollars. We believe sales would be far brisker if there were already reimbursement in place (we had a dream last night that reimbursement was in place before approval, like it was for J&J's drug-coated stents – then we woke up…) – lack of reimbursement will limit sales, and limited sales will slow reimbursement, since payors want to see patient acceptance. In one bit of exciting news, DexCom plans to submit its 7-day sensor for approval at the end of this quarter. The 7-day STS has been improved to be more accurate and stable, with a reduced needle size for insertions, increasing comfort for users, which is terrific – right now, the insertion for STS is manual, and although it's bearable, it's not painless like Insulet's automatic insertion for its dispoable Omnipod pump. We think the two go together well because both are pretty discreet, though CGM will also appeal to more patients as performance improves further. Dex Com's new sensor is fully waterproof (more good news, since no one liked shower patches) and has improved feedback screens – we imagine it will also have software, which will be very welcome (so far, software is out just for healthcare providers). DexCom also plans to direct its marketing toward larger regional centers; the company concedes that it is still learning how to market this first-generation product, which requires a new style of diabetes management.

DexCom presented the results of its three consecutive 7-day runs of the 7-day STS in a jam-packed (at 5:30 am) symposium at the 2006 AACE. The sensor showed a Mean Absolute Relative Difference (MARD is a way to measure accuracy) of 15.7% on the seventh day and that 97.2% of 6,200 data points fell into the A and B zones – better data than in its January, 2006 *Diabetes Care* piece, so good strides. DexCom also has four data sets accepted for the 2006 ADA – all of which suggest some exciting developments at the company.

INGAP – Back to the Future: Breaking news about INGAP (Islet Neogenesis Associated Protein) – This therapy, a 15-amino acid peptide sequence of INGAP once belonged to P&G, who returned the license after their phase 2 studies suggested that they would have to do more studies before going into phase 3. Some people thought that this drug would not come back even though a therapy that could cause fully functional islets to develop from progenitor cells would be a real breakthrough for both type 1 and type 2 patients. Originally isolated from hamsters by Drs. Arthur Vinik and Lawrence Rosenberg then at the University of Michigan, INGAP and later INGAP Peptide were licensed to GMP Companies, which in turn licensed the peptide to P&G. INGAP peptide has produced islet neogenesis activity in several animal models and normal animals, including monkeys. The performance of the peptide in a variety of animals generated much interest about its prospects as a neogenesis therapy. Dr. G. Alexander Fleming, former FDA head endocrinologist and an early consultant to GMP Companies, stated " …It would be a major therapeutic advance for people with T1 or T2DM if an effective neogenesis therapy could be developed. For this reason I saw INGAP peptide as one of the most promising therapies that I had come across during my 12 years at FDA and head of the clinical group responsible for diabetes therapies." INGAP therapy was subsequently licensed to Procter & Gamble Pharmaceuticals, which conducted two phase 2 studies of similar design for type 1 and type 2 subjects. Procter & Gamble reviewed the data from the three-month studies and did not renew its sub-license for the drug in March 2005, raising concerns that the trials produced negative results.

INGAP peptide was not to be abandoned, however. Fleming undertook a de novo analysis and interpretation of the phase 2 results and saw convincing evidence of efficacy and real potential of the peptide as a neogenesis therapy. Kinexum Metabolics, Inc., of which Dr. Fleming is the Chief Scientific Officer, and his partners, Mr. Kevin Roché (president and CEO) and Lisa Jansa (chief operating officer) have secured the sub-license and IP from GMP Companies and published a new interpretation of the Phase 2 data.

The results of the phase 2 INGAP studies were still largely despite problems with the trial design. Specifically, highly significant treatment effects were seen in HbA1c in T2 people and C-peptide in T1 people (and strong trend for an effect on A1c in T1, as well). Problems with the design of the study included poor starting glycemic control, no measurement of the C-peptide endpoint at the end of treatment, once a day dosing of a short-lived peptide and relatively high drop out rates because of injection site reactions from the large single daily dose. The therapy should have been given in divided doses 2-3 times/day.

Larger studies must be conducted to confirm clinical benefits, but INGAP could have major benefit for all T1 patients and some insulin-dependent T2 patients. INGAP could increase endogenous insulin secretion in T1 patients to a point where they would return to the "honeymoon" stage of the disease. It would also decrease hypoglycemia and risks of complications. T2DM patients may be able to remain on oral insulin or go off of insulin entirely. "We all understand that to get a definitive medical therapy for T1DM will require addressing both the underlying immune disorder and restoring normally functioning islets," writes Dr. Fleming. "Though islet neogenesis is a thoroughly validated therapeutic target and a flurry of supportive publications have come out lately, progress and resources in the neogenesis area significantly lag those in the immunomodulatory arena." If the INGAP therapy is approved, it will presumably act synergistically with immunomodulatory therapies as they become available. Such a combined approach could be fundamentally important to achieving definitive treatments or cures for T1DM.

ConjuChem—Fundraising…: ConjuChem (CJC) raised C$15.8 million (US$14.2 million) through the sale of 7.5 million shares at C$2.10 per share in a follow-on. Its PC-DAC: Exendin-4 is in a Phase I/II trial for type 2 diabetes. Data on this product are expected to be released next quarter. We are not holding our breath.

—By Nupur Lala, Jennifer Wei, and Kelly Close

4. Conference Report: GLP-1 at the Amsterdam Diabetes Forum

This year at the Amsterdam Diabetes Forum, presenters discussed a new target in the treatment of diabetes—incretins. Incretins, namely glucagon-like peptide-1 (GLP-1) and glucose insulinotropic polypeptide (GIP), are a class of hormones secreted from epithelial cells along the gastrointestinal tract after a meal. Incretins improve blood sugar control by increasing insulin's release from β cells (beta cells) and suppressing glucagon's release from alpha cells. Incretin treatment works in one of two ways. In one model, a GLP-1 agonist, or a drug that activates GLP-1 receptors, is administered. In a second model, a drug that inhibits the degradation of endogenous GLP-1 is given, thereby allowing more natural GLP-1 to circulate in the body. Some believe development of incretin therapies may change the paradigm for treating diabetes. Here are a few conference highlights and excerpts that explore the function of incretins and their effectiveness in treating diabetes.

Take away messages

Why incretins?

- Type 2 diabetes develops following years of insulin resistance. Normal glycemia is maintained during these initial years due to the work of beta cells, which compensate for the increasing glycemic load by secreting increasing amounts of insulin. However, insulin secretion depends

more on overall beta cell mass, not the amount of insulin secreted by any given β-cell. Individuals develop diabetes when the mass of β-cells decreases beyond a certain point as a result of either decreased proliferation and/or natural cell death. Susan Bonner-Weir, Ph.D., of the Joslin Diabetes Center, explained β-cell physiology in individuals with and without diabetes. beta cell mass increases alongside body mass (due to puberty or obesity) in order to match metabolic need. When β-cell mass no longer matches metabolic need, diabetes develops. Philippe Halban, Ph.D., of the University of Geneva, clarified a related misconception: in relation to diabetes, β-cells do not tire out after an extended period of insulin resistance. Rather, they decrease in mass and can no longer compensate for insulin resistance.

- Given this understanding of diabetes, therapies should approach diabetes management from one of two directions—either through targeting insulin resistance to improve the efficiency of insulin action, or through β-cell function (by increasing β-cell mass) in order to produce sufficient levels of insulin. The former approach involves treatments such as TZDs while the latter involves sulfonylurea, but incretin therapies may offer a new approach.
- Incretins are crucial to maintaining normal glycemia. Normally, glucagon is released from alpha cells only in the context of low blood sugar. In normal physiology, glucagon operates when the body is in a fasting state. In this way, glucagon stimulates the liver to release glucose. In individuals without certain metabolic complications such as diabetes, glucagon is suppressed after a meal by GLP-1 and insulin. However, in the context of diabetes, because GLP-1 and insulin levels are low, glucagon levels remain high, mistakenly signaling to the body that it is in a fasting state. The liver continues to supply glucose to the body when it is not necessary, leading to post-prandial hyperglycemia. Incretin therapies lead to increased levels of GLP-1, thus correcting the signal that shuts off post-prandial glucose production.

Therapies that take advantage of the role of incretins follow one of two pathways.

- Some therapies activate the GLP-1 receptor directly. Exenatide is a GLP-1 receptor agonist, or a molecule that binds the GLP-1 receptor, thereby stimulating insulin release, lowering blood sugars, and causing sustained weight loss. Natural GLP-1 is quickly degraded in the body, but agonists like exenatide are active in the body for longer periods of time. Likewise, liraglutide is a long-acting GLP-1 analog.
- Other therapies try to increase the amount of natural GLP-1 available. GLP-1 has a short half-life because an enzyme known as DPP-4 quickly degrades it. DPP-4 degrades GLP-1 that would otherwise stimulate the release of insulin and suppress the release of glucagon. By blocking DPP-4, DPP-4 inhibitors can lead to increased levels of endogenous GLP-1.
- Each approach has its own positives and negatives. Exenatide must be injected and can cause nausea, but it acts extremely effectively and can support sustained weight loss. DPP-4 inhibitors may be taken orally in single or twice daily doses, but are not associated with weight loss or nausea.
- Furthermore, both drugs exhibit few drug interactions and thus can serve as strong adjuncts to most diabetes therapies.

Incretins are an ideal target for diabetes treatment.

- Presenters agreed that incretins present an exciting new target for diabetes treatment. Carolyn Deacon, Ph.D., of the Panum Institute in Copenhagen, explained why in more detail.
- Incretins increase insulin release and decrease glucagon release. This double effect is great for people with diabetes since they do not secrete enough insulin and produce too much glucagon.
- Incretins work only after eating a meal, meaning that chances of hypoglycemia due to treatment are very low.
- Inhibition of DPP-4 will only raise the levels of endogenous incretins to a level naturally defined by the body, thus preventing the possibility of activating incretin receptors in a non-physiologic sustainable, and perhaps dangerous, way.

Integrating incretin agonists with insulin sensitizers

- One animal study demonstrated that combining insulin sensitizers with incretin agonists effectively treats diabetes. This combination reduces insulin resistance (via the former) and promotes insulin release (via the latter). A combination of liraglutide and pioglitazone, specifically, in one trial improved A1c's in severely diabetic rats by more than 50%, whereas the drugs individually improved A1c's by 21% and 10% respectively at the end of 5 weeks of treatment.

GLP-1 may preserve, if not increase, β-cell mass

- Dr. Bonner-Weir presented several studies that showed that GLP-1 preserves and increases β-cell mass in mice and rats. She suggested that GLP-1 may act similarly in humans. In one human study (*Diabetologia*, Nov 2005), four patients experienced extreme post-prandial hypoglycemia following gastric bypass surgery. The patients also exhibited hyperinsulinemia and increased β cell mass. Researchers thought this was due to the increased levels of circulating GLP-1 also observed in these patients. However, at the conference one person noted that gastric bypass surgery decreases stomach size and alters small intestine anatomy thereby increasing the rate at which food becomes accessible to the body. This increased rate can trigger "dumping syndrome" where food that rapidly enters the intestine triggers a massive release of hormones, including GLP-1.
- In one oral presentation, K. Piper Hanley, of the University of Southampton, UK, presented findings on β-cell growth and differentiation. In pancreases from fetuses aborted at eight weeks post-conception, liraglutide increased β-cell growth and differentiation by 24% compared to saline controls. Whether this growth is due to neogenesis or differentiation of ductal cells to β-cells remains unclear.
- In a second oral presentation, Roberto Lupi, Ph.D., of the University of Pisa, presented findings that exenatide could directly increase growth and function of β-cells. In isolated human islets treated with exenatide, markers of proliferation such as Ki67 and markers of β-cells such as PDX-1 increased alongside insulin secretion.
- In his keynote address, Dr. Steve Kahn explained the difficulties of measuring β-cell mass in vivo. Pancreas biopsies from diabetic patients without serious indications are difficult to access. Consequently we have to rely on functional markers of β-cells such as c-peptide levels following a meal. However, c-peptide is a very non-specific test and not always so useful. Technological advances that would allow researchers to quantify β cell mass in patients would certainly enhance our understanding of β-cell physiology in diabetes and consequently facilitate treatment development.

Conference excerpts

- On the second day of the conference, two leading experts in the field debated the more subtle mechanism by which DPP-4 inhibitors work. Matt Nauck, Ph.D., from Germany, who originally characterized the incretin effect, and Daniel Drucker, Ph.D., of the University of Toronto, a world expert in incretin biology, presented opposing positions as to whether the therapeutic effect of DPP-4 inhibition was solely linked to increasing GLP-1 levels. Dr. Nauck explained that because DPP-4 acts on other substrates in the body, the effects of DPP-4 inhibitors are likely related to other aspects of physiological changes during treatment, not just rising GLP-1 levels. Furthermore, GLP-1R agonists support weight loss because they delay gastric emptying thereby producing the sensation of fullness. However, DPP-4 does not have this effect and therefore must induce other relevant changes in addition to raising GLP-1 levels. From another perspective, Dr. Drucker explained that the effects of pharmacologic doses of GLP-1R agonists are quite different from those of high levels of endogenous GLP-1. Agonists continually activate receptors at higher than natural doses, and for longer periods of time as well. (Normally in the body, GLP-1 is active

for only a few minutes before degraded.) The effects of GLP-1 analogs cannot be equated to raised endogenous levels of GLP-1 via DPP-4 inhibitors.

- Dr. Drucker's position is based on lab research with his own double incretin receptor knockout mice (DIRKO mice). Drucker found that when only one receptor for either GIP or GLP-1 was knocked out, mice did not express varying glycemic levels because DPP-4 inhibitors worked effectively. However, when the receptors for both GIP and GLP-1 were knocked out, DPP-4 inhibitors lose their effect. In other words, if DPP-4 worked only by increasing GLP-1, GLP-1R knockout mice would not exhibit normal metabolic functioning (higher levels of circulating GLP-1 would still not be recognized.) Rather, if DPP-4 works by increasing levels of both incretins, then the absence of one does not completely inhibit normal functioning, as observed in mice with only one knockout.
- The FDA accepted Galvus (vildagliptin), Novartis' DPP-4 inhibitor, for review the morning of the symposium it sponsored at the conference! Vildagliptin binds DPP-4's active site and prevents it from working for 1.5 hours. James Foley presented phase 2 trial data on vildagliptin. A single dose of increasing sizes was administered to participants and DPP-4 activity was measured for many hours following treatment. Within 30 minutes after ingestion, a researcher observed an inhibitor effect that lasted at greater than 90% for 4, 6, 8, 12, and 16 hours for a dose of 10, 25, 50, 100, 200, and 400 mg (200 and 400 mg both saw a 16 hour effectiveness), respectively.
- From the above trial, 100mg per day was determined to be the optimum dosage. At 100mg/day for four weeks, participants of a second study exhibited raised GLP-1 levels and lowered glucagon levels, though insulin levels remained unchanged. (Surprising since raised GLP-1 levels are thought to affect insulin levels.) Additionally, patients reported improved oral glucose tests, and particular benefits when combined with metformin.
- David D'Alessio, Ph.D., of the University of Cincinnati, studied the chronic effects of vildagliptin vs. placebo, a study with implications on the role of GLP-1 in β cell growth. After 12 weeks of treatment, the drug was washed out for two weeks and GLP-1 levels monitored for lasting effects. The treatment group showed a two-fold increase in insulin and c-peptide levels, with a 40% insulin secretion increase after a meal. Insulin sensitivity was increased with decreased fasting plasma glucose and glucagons levels. The effects on A1c were modest, but D'Alessio attributed this to the fact that mean A1c of trial participants was 6.5, already very low! Discouragingly, however, the washout period normalized insulin sensitivity, glucose levels and GLP-1 levels. Vildagliptin likely does not have a long lasting effect on β cells. However, the placebo group in this study also showed significant improvements in insulin sensitivity following treatment to the point that the groups were difficult to distinguish.
- At another symposium, Merck presented data on its DPP-4 inhibitor, sitagliptin (Januvia). Peter Stein, Ph.D., showed that sitaglipin is 3000x more selective for DPP-4 than for other similar compounds in the body. Sitagliptin has a half-life of 10-12 hours, is well tolerated, and participates in few drug interactions. Data from one study presented showed that 24 hours after a 100mg dose, sitagliptin still shows 80% DPP-4 inhibition. The dose decreased glucose levels for 24 hrs, both postprandially and between meals. As with other DPP-4 inhibitors mentioned, sitagliptin is weight neutral and carries no major side effects.
- Additional studies aimed to quantify sitagliptin's effects on A1c levels. Over the course of a 12 week study involving 743 patients taking a total of 10-100 mg/day, A1c's dropped by a mean of .77% from a mean of 7.9%. Generally, greater dosage led to a greater drop in A1c and both fasting and post-prandial blood glucose. A similar trial was done to see if single dosing at 100mg could achieve the same effects. The mean starting A1c of 7.7% decreased by .56%. Greater improvement was seen among those with the highest A1c's at the beginning of the study.
- Gary Herman, Ph.D., of Merck, complemented the above studies with an oral presentation showing how a single dose of 200mg caused 80% inhibition of DPP-4 after 24 hours. Following a

meal, sitagliptin increased GLP-1 and GIP levels by 1.3 to 1.8 fold and improved oral glucose tests.

The conference seemed to focus on the opportunities presented by DPP-4 inhibitors and current research in this area. This focus likely reflects what many see as a potential future market for DPP-4 over GLP-1R agonists. Though GLP-1R analogs offer a uniquely effective treatment with added bonuses such as sustained weight loss, the nausea and administration via injection does not offer the treatment any practical lifestyle advantages over insulin. On the other hand, DPP-4 inhibitors can be ingested as a pill while still effectively reducing A1c's. We don't actually believe that matters very much since in the US, patients have gone on the drug with a vengeance, shots or not shots. With few drug interactions, it is true that DPP-4 inhibitors can serve as an adjunct to almost any diabetes treatment program; despite the highly positive press for DPP-4 inhibitors at the conference, however, DCU has a several reservations about the treatment, including reimbursement issues and, more importantly, safety concerns.

However, by no means did GLP-1R agonists get completely swept aside. Dr. Lawrence Blonde gave an inspiring oral presentation on long-term use of exenatide. After an initial 30 weeks, patients were invited to complete a 52-week extension with exenatide. All groups showed significant weight loss between 1-12kg, an average of 4.5 kg weight loss, and an average 1.1% decrease in A1c. Almost half reported mild to moderate nausea and 45% showed antibody formation (though 10-15% of those who formed antibodies at the end of the 30-weeek trial were antibody negative at the close of the extension). Those who reported nausea showed an average of 1-2 kg more weight loss than those who did not experience nausea.

Incretin therapies offer exciting new opportunities for treatment. Both GLP-1 analogs and DPP-4 inhibitors can be used in combination with almost all other diabetes therapies. In addition, GLP-1 analogs support weight loss and may even stimulate beta cell growth, though much more research is needed on this front. On the other hand, DPP-4 inhibitors can be ingested in a pill and still effectively help manage diabetes. Clearly, the biology of DPP-4 and GLP-1 is complex and much more work needs to be done!

—By Alyssa Shell and Cullen Taniguchi

5. Dining with the Marion Nestle of Just-Published *What To Eat*

As we mentioned in April's *Diabetes Close Up* we were thrilled to meet Professor Marion Nestle last month. Prof. Nestle's new book *What to Eat* is already climbing up bestseller lists; definitely head out and pick up a copy if you haven't already. Reading it before your next supermarket spree is a good idea too. *What to Eat* doesn't just inform, it advises; Prof. Nestle debunks myths and explains what makes food healthy—or unhealthy. Her previous books *Food Politics: How the Food Industry Influences Nutrition and Health* (2002) and *Safe Food: Bacteria, Biotechnology, and Bioterrorism* (2003) are both highly acclaimed. Prof. Nestle teaches in the Department of Nutrition, Food Studies, and Public Health at NYU, though she's lived, lectured, and eaten all over the country. We were fortunate enough to catch up with Prof. Nestle over a most-inspiring dinner in San Francisco to discuss diabetes, nutrition, and more. Some of the highlights of our conversation are below. We're looking forward to hearing more about *What We Eat*…and to our next food shopping trip!

On Children's Health: "Today, everybody knows obesity is a problem and everybody is worried about children. Everybody knows that marketing is a major problem too. That's a huge change from when I wrote *Food Politics* in 2002. Then, nobody talked about marketing to children and now, everybody does.

A recently completed report[1] shows that food marketing influences everything about what kids want to eat. And what they eat directly influences their weight and their health."

"Baby food is actually quite simple, for example. There are only two kinds, organic or not. And usually, there are only two brands that are priced the same. So all you have to do is decide whether you want to spend more on the organic, which I think you should. But I noticed that the last time I was in a store looking at baby foods – actually since the book came out – that the stores now sell packaged junk food for babies! But why am I so in favor of organic? The Certified Organic seal means that the foods were grown without pesticides or chemical fertilizers and the farms were inspected to make sure they follow the rules to the letter. So organics are good for the planet. I think we don't really know the long-term effects of pesticide residues and I wouldn't want to be doing that experiment on my kid. I'd pick the organic options, if I had the choice. But--why not make your own baby food? It just takes seconds to mash up a banana."

"Doctors—especially pediatricians – tell me they are seeing obese kids at younger and younger ages. If you're five years old and you're already overweight, that obviously does not bode well for future health. Parents have to work hard to make sure their kids eat well and get *plenty* of active play time. It sounds straightforward, but that's not easy if you are working all day long.

"The hopeful part is what is happening in schools around school meal issues. I see this as a grassroots, social movement. Exciting changes are happening everywhere. Parents, teachers, principals, school board members, people concerned about children's health and obesity are going into the schools to look at what kids are eating and what the food environment is like. They're horrified and they're doing something about it. They are improving the food situation in schools all over the country."

"I saw your great blog, where you had done a piece on Alice Waters (owner of Chez Panisse Restaurant and Café in Berkeley) and the terrific work she is doing in Berkeley—the Edible Schoolyard and meals in all Berkeley schools. I visited the Edible Schoolyard and was really moved to see how the program involves kids in every aspect of food, from production to eating, and uses food as a way to teach science, math, history, language, and culture—all in the context of food."

On Obesity: "In terms of obesity and weight loss, it's so hard to avoid gaining weight because the environment is set up to make it impossible. There is just so much food available everywhere, at all times of day or night, and in huge portions. All of this encourages us to eat more calories than we should. And being overweight increases the risk of type 2 diabetes and other complications. So the important issue these days is your body weight. If you're gaining weight, you're eating too much. It's not any more complicated than that. If you want to do something about weight, you need to eat less, move more, eat fruits and vegetables, and try not to eat too much junk food. This isn't rocket science. But the vast majority of the country – and increasingly, the globe -- is overweight. I'd say that food marketing has a lot to do with that but we'd also make a lot of progress if we ate less, moved more, and made sure to eat plenty of fruits and vegetables.

"Behavior can't change unless the environment changes because the environmental cues to overeat are too strong. There's now plenty of research showing that large portions encourage people to eat more calories. The more times a day you eat, the more calories you eat. The closer food is to you, the more you'll eat it. These are environmental cues that hardly anyone can overcome. Cheap prices also encourage us to eat more. But larger packages are the most serious problem. Anyone presented with a large package or a large portion will eat more calories from it. The people who are researching such factors conclude that

[1] References National Institute of Medicine paper titled "Food Marketing to Children and Youth: Threat or Opportunity"

the environmental cues completely overpower any thoughts you might have about what it is you're supposed to be eating or how hungry you actually are. We're going to eat what is in front of us, and what's in front of us creates major problems when it comes to obesity."

On Type 2 Diabetes Treatments: "I worry about drugs because they all have side effects, and it's only a matter of time before you find out what they are. Some fraction of people will react badly to drugs, and drugs are expensive, given our healthcare system. So if you're taking a drug and you're losing weight and that helps you control your blood sugar, I think that's great. But the object of the game should be to get off the drug. Again, my advice is simple: eat less, move more, eat plenty of fruits and vegetables and don't eat junk food. For somebody with diabetes, losing just a little weight will go a long way toward getting the blood sugar numbers under control. But the environment doesn't make it easy for any of us to do that. Right now, the default is to eat *more*, move *less*, and eat lots of *junk food*. We have to change that default."

On Exercise and Nutrition and Making Statements: "Once you're in a car, then you're caught up in a convenience mentality. You want to park as close to where you're going as you possibly can. Should you bother to tell someone to park at the end of the parking lot? Nobody is going to do that. Instead, it has to be easier and more acceptable for people to walk. The public health people who are trying to figure out how to encourage people to be more active are talking about this in terms of what they call the "built environment"—wide sidewalks, attractive stairwells, neighborhoods with plenty of activity. It's interesting. I went to at town hall meeting in Berkeley when I was teaching there during the spring that was all about gyms as the way to increase physical activity. I don't think gyms work for very many people. It was an absolutely gorgeous day, the first one in months of rain, and yet the gym was full of people on treadmills. Go outside! Walk from here to there and admire the flowers!" (Ed. note – Nestle practices what she preaches. After dinner, we dropped her at BART, which is how she got to San Francisco, from Berkeley – in all, before our dinner, she had walked several miles in Berkeley and San Francisco, clearly without giving it another moment's thought. Nestle lives in New York City, doesn't have a car, and walks everywhere. She walks the requisite 5 miles a day in the normal course of daily activities. "That's one of the great things about living in New York," she says. "Being this active is just normal if you don't have a car.")

"Everybody worries about protein, but I don't see protein as an issue. Practically anyone who eats enough calories gets enough protein. It's pretty hard not to, so much so that most people eat twice the protein they need."

"I think people should be speaking out, exercising their first amendment rights to complain about the way food is produced, and enjoying their dinner -- and I want people to be active physically and politically. The wonderful thing about food is that by making some simple changes in the choices you make, you can make a huge difference in people's lives. The best example is seen in schools that are improving the food service. Making that happen is very empowering. People can feel helpless to do anything about the war in Iraq, or climate change -- these are enormous issues. But every single time you order something in a restaurant or buy something in a supermarket, you're voting with your fork. You're making a statement about the kind of world you want to live in through the kind of food you want to buy."

—By Aviva Gilbert, Erin Kane, and Kelly Close

6. P**re-ADA, Chatting with Dr. Steve Edelman …**

For the fifth interview in our series, we spoke to Dr. Steve Edelman, Professor of Medicine in the Division of Endocrinology and Metabolism at UCSD, leader and *founder of Taking Control of Your Diabetes, a not-for-profit organization that assists diabetic patients in diabetes management*. He is Co-Director of the Endocrine Fellowship Training Program at UCSD and the Veterans Administration

Medical Center in San Diego. Dr. Edelman serves as a member of the ADA Professional Practice Committee and the Self-Assessment Subcommittee of The Endocrine Society. He was diagnosed with type 1 diabetes at 15 and is today a highly regarded local and national leader in diabetes treatment, research and education. We recommend that any reader who is unfamiliar with his organization, "Taking Control of Your Diabetes," attend one of his conferences to better understand both the patients and the medical leaders of this field. The author of two books and more than 100 journal articles, Dr. Edelman is a reviewer for numerous professional journals, including The New England Journal of Medicine and Diabetes Care. Dr. Edelman earned his medical degree at UCLA, with honors, and his undergraduate degree UC Davis (no slouch, he was valedictorian of his class) and completed his internship and residency in internal medicine at UCLA. He subsequently completed a fellowship at the Lahey Clinic in Burlington, Massachusetts; a clinical fellowship in endocrinology and metabolism at the Joslin Clinic in Boston; and a research fellowship at UCSD. Several days before the start of ADA 2006, he generously spent time with us sharing his views on the latest tools in diabetes care.

Kelly Close: Thank you so much for taking the time to speak with us, Dr. Edelman. To start off, I'm curious about what patients are asking you about these days. What are they excited about? What are you excited about? What has changed in terms of what people are asking you?

Steve Edelman: Well, a lot of people are asking about inhaled insulin, the DexCom sensor, the Abbott Navigator, and the Medtronic MiniMed Sensor-Augmented Pump. There's a lot of interest out there about the Amylin products, because doctors are hearing from patients about it and vice versa.

KC: What do you think about pumping in light of continuous monitoring?

SE: I think the pumps (both disposable and traditional) will make it easier to act on the numbers people see on continuous monitors. I think everybody with type 1 could benefit from continuous sensing, whether they're on a pump or not. I'm not sure if that's going to drive more people to pumps, but I think people, regardless of whether they're on a pump, will benefit greatly from continuous monitoring.

SE: One problem with traditional pumps is faulty infusion sets, where the insulin leaks out at the surface and leads to unexpected hyperglycemia – that happens more than you think. Air bubbles are another problem. I think the biggest issue is that people disconnect for too long, so even if their blood sugar isn't that high when they reconnect, they're relatively insulinopenic. As a result, they do not respond the same way to subsequent boluses for meals and they end up high. Insulet, by the way, avoids that problem since there is no tubing people keep it on 24/7 and disconnection is not possible.

KC: Switching gears just a bit - is there anything you can say about continuous monitoring? Can you talk about how it compares to your initial expectations, and whether you think it has the potential to revolutionize management?

SE: Without a doubt, it definitely has the potential to revolutionalize management for type 1 patients. There's no question that most type 1s will do better having the DexCom STS or any other type of reliable continuous technology available 24 hours a day. It will reduce the standard deviation of blood sugars, reduce the wide fluctuations, protect against hypoglycemia, and it will allow type 1 patients to reach A1C levels that are closer to 6 percent much more safely. There just need to be reimbursement policies in place.

KC: Back to continuous, which is what we've got for now. So imagine that you could focus on just one group of patients initially. What groups of patients do you think would benefit the *most*?

SE: First I would focus on all gestational and pregnant type 1 patients. As you know, control is so important during gestation. Just think how much money people will save by keeping babies healthier, versus in the hospital … Right now, the need for C-sections is high because babies are too big, and there are so many other risks in this population as well. Then, I would say, type 1 patients. Even though I see a lot of people who are proactive in my practice, it is a rare person with type 1 who wouldn't benefit from continuous monitoring. With type 2s on insulin, perhaps loaner continuous monitors would be helpful. They could experience continuous monitoring for a week every quarter or so. Just *think* what overweight type 2s who are not really under good control would experience. They could see how high they get after meals and what exercise does to help their diabetes – continuous is an outstanding behavior modification tool.

KC: Absolutely…

SE: Related to treating with CGM, one thing I've realized recently is that we have to get today's insulins to work as fast as IV insulin. That's the next challenge.

KC: Switching gears, you're down in San Diego, and that always makes me think of Amylin, which so many people in industry and in the investment community – as well as doctors and nurses – would love to hear your view on. What can you say about Byetta and Symlin, now that both drugs have been out for a year-plus?

SE: Byetta is easy. I'm not surprised at all with the rapid uptake and growth of prescriptions - it's a blockbuster all the way, from start to finish. LAR will just make it even stronger. Primary care doctors are even using it a lot more than you'd expect, being a new injectable agent.

KC: Do you think that this is something that's empowering primary care doctors?

SE: I think primary care is picking it up much faster than anybody would have predicted.

KC: Do you think it's because it's very easy?

SE: First of all, Byetta makes most people lose weight. Second, Byetta is very effective at lowering blood sugars. The pen helps quite a bit as well in getting over "injection phobia". Patients also don't have to test their blood glucose values any more than before. So, you don't have to teach them *anything* else – you just have to give it to them.

KC: Are some patients, once they become comfortable with it, testing less because they're doing better?

SE: Oh, yes. Absolutely.

KC: I also understand that some doctors are prescribing it more than two times a day, for the people who don't really mind the pen injections, in order to improve fasting blood glucose, and to reduce nausea. Have you tried that with any of your patients?

SE: I have had a handful of patients do that who could not tolerate the 10 mg dosage. So I give 5 mg three times daily and it works very well.

KC: And is the response to it even a little *better*, because it works better on the fasting and it may help the nausea a little bit more?

SE: Yes, and the patients get more coverage too. I also have a patient on 10 mg three times a day who is experiencing better results. Amylin most likely did not study a TID regimen as it may have been too much to ask people to take Byetta more than twice a day. That's one reason why the LAR is going to be so effective.

KC: Some wonder whether people might be discouraged by the large size of the LAR needle and whether they might therefore prefer to take Byetta a couple times per day. Of course, this is pure guesswork since it hasn't been announced what the actual gauge of the needle is. But that never stops speculation …any thoughts whether patients might be especially put off by the gauge of the pen needle that will be used with LAR?

SE: I don't think so.

KC: No?

SE: A lot of people going on LAR may never have given themselves an injection before so they won't have any biases. The injection with the smaller gauge needle (i.e., larger needle size) is not limiting. Think about the needles we used to use for diabetes not all that long ago.

KC: Very true – and you're right, we didn't really question it. Anything to get insulin – how far we've come! So can you talk about the weight loss experience? How much weight have patients lost and what has their response been to it?

SE: Kelly, I'm not kidding you, I've had at least five patients who have lost close to 40 pounds to 50 pounds.

KC: Wow. Amazing! This is diabetes treatment, 2006 – how fantastic!. The world has changed and we probably really haven't begun to realize the magnitude.

SE: I just saw a patient today who lost 50 pounds. I've also had a couple people who have lost less as well - that's when I usually go to 10 mg three times a day.

KC: Wow – it's so great to see how doctors are really using this drug. It sounds like it has empowered both patients and doctors, which might be why we keep hearing the real-world experience and outcomes with Byetta are often better than those in the strong AMIGO trials. So switching gears, what do you think about Symlin now that it's been on the market a year and a few months? What's your take?

SE: Despite the uphill battles - you can't mix Symlin with insulin, you have to inject it, you have to deal with the rubber cement tops that dull needles, the potential for nausea, the need to titrate the insulin and Symlin… despite all that, the market share will grow. The *vast* majority of my patients who have started on Symlin have benefited from it tremendously. You must pick your patients wisely.

KC: Mmm, I get it and I can see how important that is, today being someone who cannot now imagine life without Symlin, but who a few years ago, in trials, struggled with the initial nausea. I wear it in an Omnipod –ostensibly I was doing fine pre-Symlin, being under the a1c goal, quote unquote, but … I really wish we had goals for glycemic variability, because that has made an enormous difference. But, who knew? The FDA certainly doesn't seem to be convinced by anything except A1c[2]. So, whom do you pick in particular for Symlin, knowing all this?

[2] So not to diss the FDA, but really … from a patient perspective, that Symlin can really improve quality of A1c has been my big takeaway – again, who knew? And how could the agency not ask this question, having all the data? It seems reductive to just look at A1c, though of course

SE: I tell my type 1s, "This hormone will help reduce your fluctuations and make your insulin dose a little more predictable and help you lose weight if you want to lose weight." I also tell them that it's not really going to lower their blood sugars dramatically either. I tell them, "That's not the main purpose of it. The main purpose is reducing variability." For type 2s I primarily stress weight and blood sugar control, and then I have them read about it and let me know if they want to start it. Patients are losing much more weight than they did in the clinical trials.

KC: Right. I wonder about Byetta and Symlin off-label, because a lot of people do want to lose weight.

SE: Symlin works very well in people who have had gastric bypass who are scared to death because they're gaining the weight back. Symlin will work on obese type 2s while on insulin or oral agents.

KC: Interesting.

SE: I have a bunch of patients on it, and it really works. The other group that I've been using it in is basically non-diabetic obese patients. People have lost a ton of weight. You just have to use higher doses.

KC: In terms of just thinking about diabetes patients, what do you think the standard of care looks like now for type 2s? How has that changed with the availability of GLP-1 and how would you expect it to change with DPP-4s, and with inhaled insulin and with LAR?

SE: [*Laughter*] That's a big question. I still think that the standard of care for most type 2s is going to be metformin first, and hopefully TZDs or Byetta second, but I think it's going to be slow going. I think patients are going to be tried on oral medications first. I do think the DPP-4s might be beneficial if used very early in the natural history of diabetes but it is a challenge because they're going to be a lot more expensive than metformin and sulfonylureas for sure, and probably TZDs.

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hindsight is so 20/20. My experience – and this is n=1, but I hear the same thing from other Symlin fans, so it's not really n=1, it's at least n=a dozen! – I know that's still small – so when you are diabetic, take insulin, and have a decent A1c, you don't know how relatively bad you feel until you get Symlin and figure out how to stay on it. and then, one day, there's a breakthrough and you realize, my god, I feel so different than I did. That's my experience and I don't think it's so uncommon for hyperintensively managed patients who have the time to go on this. And definitely, it took some time to get there–now, I can't imagine not being on it – my quality of life would suffer meaningfully. That Symlikn was nearly not yet approved is unbelievable to patients like me who have benefited so much in terms of many fewer spikes, though not necessarily so much in terms of lower A1c. Check it out – I'm so lucky to meet so many patients and parents of patients in my work, and I received a note from a mother of a child recently who was asking about glycemic variability – her words were poignant, and so on: "*I will read the glycemic variability work you have sent – thank you. I don't know much about it but it just seems like it must be so important not to have your glucose shooting up right after meals, I don't know what all the debate is about? Intuitively, it's just obvious that this cannot be healthy."* Exactly. How can spikes and valleys that add up to a perfect score be healthy? I wonder if we will eventually find patients and even doctors and nurses have been misled, thinking that A1c is everything. It's so critical, as a marker, but not the full story. When patients find out Symlin is a missing hormone, of course it makes sense. It makes me upset that I've been missing it so long. But for sure, I can understand the challenges in going on it – I'm lucky because my insurance covers it (this hasn't been a big problem actually, it seems, for anyone with insurance), and I had the time and understanding to stick with it through the nausea. It reminds me of an analogy with my husband – whenever he gets back from a run, he exclaims no end about how *great* it is, how amazing the endorphins are, how he's dying for me to take up running with him (this is about one zillion years into our relationship!) I always say with a twinge that it's not for me, I don't get running, I don't love it, I don't have it in me. He tells me I *have* to try it for a few months! And then, magically, I too will be addicted! I always buy it, but can never really get it together to change - which only speaks to my laziness! This seems similar – not about laziness, but just about things taking time, and some patients will be motivated, and some won't. My bet is that as the glycemic variability body of evidence continues to grow (see our last issue for more on that, and the important Monnier work in type 2s and the accompanying JAMA editorial by Drs. Hirsch and Brownlee), this will be convincing. Symlin takes some time and I so didn't get it at first, physiologically – just intellectually. Now, I couldn't go off it – not just because I've been lucky to be exposed to the body of evidence is growing about the dangers of glycemic variability and oxidative stress, but because after some time, it just made me feel so incredibly much better. I talk to patients on it who have stayed on it (and that's not that easy – though it will be far easier now that real-time continuous monitoring is emerging) and they don't even know why, but they say going off it would really worry them – they don't want to go off, but they can't articulate why. I'm like that too. These are small patient numbers now, but they are growing. I can tell even when I go off it for a day that I don't have Symlin working. It's a secret weapon and god knows, we've needed one. It's our time, like Dr. Joe Prendergast says (www.endocrinemetabolic.com).

KC: That's interesting what you said about TZDs, in light of the forthcoming big outcome trial presentations later this year at EASD and IDF – DREAM and ADOPT. What do you think about TZDs for impaired glucose tolerance, for example?

SE: I think they're going to have a whole new life once the DREAM Trial is presented in Copenhagen on September 15th. There's *no* question. I think their day is coming again. I like them. I think it's an important class, because they attack the main defect of type 2 diabetes.

KC: The insulin resistance?

SE: Yes.

KC: Do you think that evidence in support of the beta cell regeneration will emerge for TZDs, GLP-1, DPP-4s? Can you talk about what trial you would want to see?

SE: I'm a big believer that the TZDs do preserve beta cell function. Just look at the secondary failure rate on these long-term extension studies.

KC: Can you speculate at all about beta cell regeneration in GLP-1 and DPP-4s?

SE: There is lots of animal data and surrogate marker data suggesting beta cell preservation in GLP-1 and DPP4s…

KC: Can you talk about Taking Control of Your Diabetes a little bit? (Editor's note: Taking Control of Your Diabetes (TCOYD) is a nonprofit organization based in San Diego and led by Dr. Edelman. Its mission is to educate and motivate people with diabetes and their loved ones, to take a more active role in their condition, in order to live healthier, happier, and more productive lives. Find out more at www.tcoyd.org.) What kind of challenges have you seen, how have the challenges for patients changed over time, and how has patient behavior changed over time?

SE: Right now our conferences are getting bigger and bigger, and more and more people are realizing that it's their disease and they have to get educated. At the conferences, we encourage people to get smart so that they can work with their caregiver. We do not encourage people to go stomp on their caregiver's door and say, "How come you haven't given this to me?" We try to teach patients to *help* their caregiver take better care of them. But it's difficult – it's been slow going, Kelly. Patient education is a very tough area.

One thing you will realize if you just walk around the conference and read patients' expressions and listen to their comments, is that people are really thirsty for information. Every conference we put on costs our organization approximately $175,000, and our registration fee is $25 to $35. Our average attendance is a little over a thousand right now. Just $35,000 to cover $175,000 in costs.

KC: Yes – but to make it accessible is so necessary, isn't it? Wow, you have to get a lot of other funding for this. Everyone should go to your website this instant (www.tcoyd.org) and give a donation!

That's what nonprofits are for, and that's what we do with the grant money we receive. We apply for government grants and pharmaceutical unrestricted educational grants. I'll tell you, it's so gratifying to be able to help people – and it's very sad to see what's out there for people who have not had access to good care. It's super sad. I met a 27-year-old woman who is basically blind who was at our Des Moines conference recently - so many people there in wheelchairs, people with strokes. A lot of these people never had access to good healthcare.

KC: The obvious question, of course - what could industry do to help?

SE: Well, many companies have been very supportive but in general more money is spent on professional education compared to patient education. TCOYD would be able to help more if we had greater funding.

KC: A no-brainer …

SE: And I would urge them to try to promote their drug assistance programs a little bit better.

KC: My last questions are on a more personal note. What's it like to practice in endocrinology today versus ten years ago? How does being a person with diabetes inform your own interaction with patients? Where do you see the future of endocrinology, and what trials are you looking forward to as your own research continues?

SE: I'll answer that last part first. To me the most important thing is putting more emphasis on prevention of type 2 diabetes. We already know several methods to do it, including lifestyle and TZDs, metformin, xenical and acarbose – we have a whole list of drugs, but we don't have any formal indications for prevention, and we don't have any good screening tools. The next decade will be the decade of prevention trials. There are a whole host of them, as you know, coming out. I think we *have* to work better at diagnosing people earlier. Like for example, getting a pre-diabetes diagnostic lab test that includes insulin and glucose ratios. I think that's where the future lies, in prevention.

I would love to see some headway in prevention of type 1 as well. Type 2 is the bigger problem, obviously.

I know type 1s who are doctors and they purposely stayed away from endocrinology because they don't like being reminded about their diabetes on a day-to-day basis. I would say for me, personally, it's helped me create a much closer bond with my patients as I can understand what they're going through. I'm the kind of person who has probably never passed judgment on high blood sugars and high A1Cs, because I've been there.

KC: Right. Absolutely … from a patient perspective, I can say it makes such a big difference when your team really understands what it's like.

SE: Treating diabetes today is so much easier than ever before, because we have so many tools, but it is hard because managed care has just put a damper on everything. I cannot treat patients the way I trained to do so in medical school, residency, and fellowship. It's so frustrating being a doctor today in a managed care environment, especially like in San Diego. That's one reason I started TCOYD. As a doctor I felt helpless, but as a "covered life" I have more power.

The ultimate goal is to prevent diabetes in the first place. Our country needs to be more supportive of non-pharmacologic therapy, which is really works well, and more supportive of culturally- and ethnically-sensitive dietary intervention and exercise. Being an investigator myself for seven years, I learned from the diabetes prevention program that you can't just tell people to do it. You need to give them support and you need to give them things like pedometers. You have to take them for walks, you have to create support groups, and you have to create competition between groups. It can be done, but it doesn't come cheap. That would be a big payoff.

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sensitive dietary intervention and exercise. Being an investigator myself for seven years, I learned from the diabetes prevention program that you can't just *tell* people to do it. You need to give them support and you need to give them things like pedometers. You have to take them for walks, you have to create support groups, you have to create competition between groups. It can be done, but it doesn't come cheap. That would be a big payoff.

KC: That's such an integral part of the message of Taking Control of Your Diabetes. Thank you so much for all your leadership on this front for patients across the globe. There's just no one like you. Thank you so much for talking to DCU – we'll see you at the TCOYD conference in San Jose in October!

—By Kelly Close

7. CONFERENCE REVIEW: AACE HIGHLIGHTS

1. **DexCom presented new data in the poster session for their 7-day sensor,** and these accuracy figures trumped what had previously been shown for their 3-day sensor. There was a correlation coefficient of 0.899, with 97.2% of points in the Clarke error grid A+B zone. The mean and median ARD were, respectively, 15.7 and 11.4.
2. **Overall, the symposia were heavy on practical issues of diabetes management**—the majority included case presentations, and we heard from more than one speaker on issues of coding for reimbursement. Dr. Scott Lee addressed reimbursement for CGM and pump training, suggesting that physicians need to code strategically to make time spent on these areas affordable.
3. **The speakers at the Novo Nordisk symposium on initiating insulin therapy were extremely positive on premixed insulin**, and we have heard from other HCPs who advocate the use of premixed insulin in patients with type 2. These presentations included references to a number of studies, which we found helpful. One criticism of these studies as a whole that we have heard is that the long-acting insulin is given only once daily, while the premixed insulins are given twice daily. In fact, though long-acting insulins are sometimes split into two parts, we think most patients on basal insulins take them once daily, so we believe these trials are reflective of the ways the two therapies are given. While type 2 patients may not like taking two shots a day, premixed insulins may be a better option than a basal-bolus regiment requiring four shots each day.
4. **Dr. Ronald Kahn, President of the Joslin Diabetes Center, has discovered a new gene that appears to play a key role in type 2 diabetes.** The ARNT (aryl hydrocarbon receptor nuclear translocator) gene is a transcription factor involved in response to conditions of hypoxia and other environmental conditions. Dr. Kahn's lab has created a mouse where they have eliminated this gene, and the mice lost first phase insulin secretion and developed impaired glucose tolerance.
5. **In her update on the consensus on diabetes and pregnancy, Dr. Lois Jovanovic noted that the Hyperglycemia and Adverse Outcomes of Pregnancy (HAPO) trial will have results in 2007.** It is a multi-center study intended to determine the threshold above which problems begin. Until then, providers should normalize blood glucose.
6. **Giving the first positive take on TZDs that we've heard in a while, Dr.** Bob Henry argued that they restore lost adiponectin function in patients with type 2, which is linked to cardiovascular benefits. Dr. Henry reminded the audience that the fat cell is an active endocrine organ, with more than 30 different secretions, including FFA, CRP, adiponectin, resistin, leptin, TNF-alpha, angiotensin II, and IL-6. As adipose tissue mass increases, so does production of all of these things, with the exception of adiponectin, which decreases.

7. **At the Abbott-sponsored symposium on continuous glucose monitoring, Dr. Howard Wolpert suggested that patient education to minimize risk for hypoglycemia** from over-bolusing entails understanding of insulin pharmacodynamics versus pharmacokinetics, appropriate utilization of pumps with bolus calculators to minimize dose stacking, and understanding of factors that affect postprandial glucose patterns, including the different effects of low glycemic index carbs and high fat meals. Dr. Wolpert has developed an education program for patients in his program who use CGM.
8. **Dr. Irl Hirsch called the isoprostane 8-iso-PGF2-alpha " the hemoglobin A1c of oxidative stress."** It is the most commonly measured F2 isoprostane. It is an indicator of free radical production derived from esterified aracadonic acid and was the marker measured in the recent paper by Monnier and colleagues in *JAMA*. Dr. Hirsch stated the significance of the understanding of glycemic variability (GV), saying that it 1) suggests that therapeutic strategies should be targeted at controlling GV; and 2) indicates that CGM should be used to minimize GV and superoxide overproduction.
9. **With its recent STS launch, DexCom was the center of attention.** Their booth drew a lot of attention on the exhibition floor, and their Saturday 6:15 a.m. breakfast was packed, despite the early time.
10. **In a Lilly-sponsored symposium on incretin therapy, Dr. Carol Wysham presented some amazing case studies from the long-term extension trial of exenatide;** she had patients with an A1c reductions of 3.2% and weight losses of 45 pounds. Despite this, Dr. Wysham said that about 10% of patients do not have significant initial response. In the clinical trials, approximately 25% did not lose weight. Of those that have initial response, approximately 15% of her patients have experienced a gradual increase in A1c and weight after 1-3 years. Dr. Wysham said also that approximately 10% of her patients cannot move from 5 micrograms to 10, and another 10% cannot tolerate either dose.

—By Erin Kane and Kelly Close

8. Coming IPOs—HDI?

After TheraSense went public in 2001 and was sold to Abbott in 2004 ($1.2 billion) and after Animas went public in 2004 and was sold to J&J in 2005 ($525 million), there have been fewer exciting public "pure plays" in diabetes devices. Outside Amylin and Mannkind, there aren't any on the pharmaceutical side and few on the device side. However, that may be changing. Rumors of various diabetes companies gong public abound and we believe much is possible, given the demand for investment vehicles focused on diabetes – in our view, for example, Insulet could go public tomorrow, as could Metabolex – no doubt the companies want to optimize timing, but we certainly think the market would be receptive. One company that has already filed is Home Diagnostics, Inc. (HDI), which filed to go public in May, 2006. HDI is offering common stock (the number of shares has not been disclosed) and according to its S-1, hopes to use the proceeds to redeem all outstanding preferred stock, to purchase manufacturing equipment for new product development, to repay outstanding indebtedness, and for general corporate purposes.

HDI has focused exclusively on the diabetes market since its inception in 1985. HDI develops, manufactures, and markets blood glucose monitoring systems and disposable diabetes supplies, with a focus on cheap meters and strips. It markets its products under its own HDI brands (SideKick, TrueTrack Smart System, TrackEASE Smart System, and Prestige IQ) and in a co-branded format. HDI believes that its unique co-branding strategy provides the company with a competitive advantage. The company has two manufacturing facilities, one in Florida where it manufactures blood glucose test strips, and one in Taiwan, where it assembles its blood glucose monitors.

Net sales in 2005 were $100.2 million, an increase of 18% over the previous year – clearly, there's demand for inexpensive meters, particularly from mail-order, which itself is the highest growth segment of the market currently. Increases were mainly driven by higher sales volume, with a smaller contribution from price increases. The increased sales volume was driven by higher sales of the TrueTrack System (launched in 2003) and the introduction of the SideKick system in August 2005. Net income was $5.9 million and gross margins were 58.9% in 2005.

HDI hopes to become a leader in the blood glucose monitoring market by leveraging its technology to develop additional innovative monitoring products and by increasing its penetration of international markets. The company says its current R&D efforts are focused on new products that incorporate new features into existing products and new technology platforms that will expand its product offering. For example, the TrueTrack element will target cost-sensitive customers with its low-cost biosensor technology – we'll be eager to see this.

There are risks in BG monitoring, so we're cautious. Growth has been terrific, but pricing pressure is high – they've actually been driving the pressure, but how low will it go? Obviously it hurts them and the market. Although the market is growing in terms of people, pricing pressure and competition are intense. HDI may be squeezed as it faces competition from large, well-established medical device manufacturers with significant resources on the one hand and from low-cost, predominantly Asian, producers on the other. To succeed, HDI will have be on the absolute cutting edge of technology and develop best-in-class products ahead of its competitors – that's a lot that has to go right, long-term.

—By Rachael Hartman and Jennifer Wei and Kelly Close

9. Literature Review: Chest hospital data
Krinsley JS, Jones RL. "Cost Analysis of Intensive Glycemic Control in Critically Ill Adult Patients." Chest. 3 March 2006. 129 (3) 644-650.

While studies in recent years have shown a benefit of intensive glycemic management on mortality and morbidity in critically ill patients, reported here is the first cost analysis of this intervention. The authors of this study, Krinsley and Jones, are the Director of Critical Care and Chief Financial Officer, respectively, of Stamford Hospital in Stamford, CT, where the study was conducted. In a 2004 study on the effects of intensive glucose management in adult medical and surgical patients, Krinsley found that a protocol targeting a glucose range of 80 to 140 mg/dL lead to a 29% decrease in mortality and a reduction in the development of new renal insufficiency and the number of patients requiring RBC transfusions. Using data from the same 1,600 patient study, Krinsley and Jones more recently assessed the changes in cost of care associated with an intensive glucose management intervention.

Study participants included 1,600 patients admitted to the Stamford Hospital ICU between 2002 and 2004. The 800 patients in the baseline population were admitted to the ICU before the institution of an intensive glucose management protocol, and the 800 patients in the treatment population were admitted after the protocol was instituted. The intervention used in the treatment period was intended to maintain blood glucose levels between 80 and 140 mg/dL.

The baseline and treatment populations were similar in terms of age, gender, race, distribution of admitting diagnoses, prevalence of diabetes, and APACHE II scores. 40.6% of patients in the baseline period and 33.6% of patients in the treatment period underwent mechanical ventilation at any time during their ICU stay. 36.5% of patients in the baseline period and 28.8% of patients in the treatment period required mechanical ventilation at the onset of their ICU stay.

Patient days in the ICU, ventilator days, and post-ICU hospital length of stay were lower in the treatment period than in the baseline period. ICU length of stay (LOS) declined from a median of 2.0 days (interquartile range [IQR], 1.0 to 4.3) during the baseline period to 1.7 days (IQR, 0.9 to 3.5 days) during the treatment period (p=0.005). Among patients not requiring ventilation, LOS decreased from a median of 1.5 days (IQR, 0.8 to 2.5) to 1.3 days (IQR, 0.8 to 2.3), although the decline was not significant (p=0.138). Among patients requiring ventilation, there was also a nonsignificant decline (p=0.222) from a median of 4.2 days (IQR, 1.6 to 9.6) to 3.4 days (1.6 to 9.2). 712 ICU patients from the baseline period survived, compared to 731 survivors in the treatment period. There was a 33.2% reduction in the total number of calendar days of mechanical ventilation and a 34.3% reduction in the total number of hours of mechanical ventilation in the treatment period compared to the baseline period. Per patient, duration of mechanical ventilation decreased from a median of 2.0 days (IQR, 0.7 to 7.1) in the baseline period to 1.7 days (IQR, 0.6 to 5.3) during the treatment period (p=0.045).

Total resource costs—laboratory, pharmacy, and diagnostic imaging costs—also decreased in the treatment period. Resource costs decreased significantly among ventilated patients in the treatment period and nonsignificantly among nonventilated patients. The cost reductions were driven by large decreases in laboratory and imaging costs.

The net annualized adjusted total cost savings during the treatment period amounted to $1,339,500, or $1,580 per patient. The greatest savings occurred among the surgical, cardiac, and GI groups, while there were net deficits among the septic shock, miscellaneous medical, and respiratory patients. The largest deficit occurred among the patients with septic shock, which was a small group (43 in the baseline period and 45 in the treatment period). However, the mortality rate among this group was nearly twice as high in the baseline period than in the treatment period (60.5% vs. 33.3%, p=0.020)! Thus, the authors speculate that the higher costs among septic patients in the treatment group may have been due to what they call a "subset of new 'expensive' survivors." The authors also report that their calculated quantity of savings may underestimate the actual savings of intensive glycemic management, as some ICU resources and costs were not included in their analysis.

Several strengths and limitations of this analysis are noted. The authors used a robust and powerful ICU database, dating back to 1998, which now includes detailed information concerning over 6,500 consecutive ICU admissions. The database measures length of stay and ventilator duration in 0.1-day units, thus greatly improving accuracy over use of calendar-day units. Also, the director of critical care or his associate performed all APACHE II scoring, thus ensuring accuracy and consistency. One limitation is the before-and-after, not randomized, controlled prospective design. However, the patients in the baseline period and the patients in the treatment period were well matched. While the number of patients on mechanical ventilation at onset of ICU admission was higher in the baseline period, the authors report that the cost analysis was adjusted for this difference. Another limitation is that resource costs were estimated instead of being calculated directly from known figures.

Krinsley and Jones demonstrated in the past that intensive glycemic control in critically ill adult patients is beneficial to patient morbidity and mortality, and in this report they demonstrate that this intervention is also associated with substantial cost savings. Extending the cost savings to other ICUs around the country could amount to major savings and monetary relief for the U.S. healthcare system. The findings in this study support adoption of an intensive glycemic management protocol as a standard of care in the ICU.

—By Katelyn L. Gamson and Kelly Close

10. Upcoming Conference Preview (fees go up after June 30 for both EASD and IDF, so click over!)

- **AADE – In LA, August 9 – 12. Our favorite meeting every year to find out what patients are really thinking.**

- **EASD – September 14-17 in Copenhagen (www.easd.org). Big ticket item – DREAM trial results, September 15, presented by Dr. Hertzel Gerstein. Be there or be square (or read our blog). This will be incredibly interesting fodder for pre-diabetes - the study purpose was to determine if ramipril and/or rosiglitazone would prevent the onset of type 2 diabetes, and this study has been highly, highly awaited…Fees go up July 1**
- **IDF – December 9-12 in Capetown (www.idf2006.org). Another long-awaited trial, ADOPT, will be presented here. This and then, the wine – it's hard to say no, isn't it?!**