DIABETES CLOSE UP

Diabetes Close Up
July 2006, No. 59
ADA 2006 Download – Move over, insulin …

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

From the Editor:

ADA was excellent! So I just had an outstanding dinner with a leader in glucose -monitoring who missed meeting and he asked me (it's now just seven days after the conference) what the biggest news was, and I look at him incredulously, as if he was from another planet. I felt so sorry that he had missed all the excitement but alas, he had been in the far east. "Wellllll, Byetta!" I finally stammered, after a delayed reaction. Isn't it obvious? Doesn't everyone know what a hit the drug has become and how the ADA this year could basically have been renamed TBS (The Byetta Show)? The man smiled, for he really couldn't help himself. "I'm so thrilled to have a hit in our field. Patients need so much help, and this is the first breakthrough for type 2 patients in such a very, very long while." Yes. More on Byetta and the incretins inside: why Byetta is still tiny today compared to how huge we think it will be, why we like (think commercial) and *dislike (think clinical) DPP-4 inhibitors more than we did before the meeting, why the weakness of the competition (for diabetes therapies in general) has the class soaring, why tolerability matters for the class, why we think the Novo liraglutide data held up more than we thought it would, and why the insulin manufacturers seem to be, at least a tiny bit, running scared.*

And that's just incretins! This is your ADA download – in addition to 20 global meeting conclusions, we cover blood glucose monitoring (LifeScan's Ultra 2 – what a launch!), continuous monitoring (SRO at Abbott's symposium), insulin pumps (Medtronic's sensor-augment pump launches and Insulet continues to draw attention), insulin (nothing new except VRAI – Biodel's very rapid acting insulin), and TZDs (let's pause as we all wait for DREAM). THEN, we download for you the Banting Lecture (all the smartest people at the meeting this year pointed to inflammation as the highlight – let us translate) and the Presidential Lecture – these were inspiring, indeed. Our PhD/MD superstar Cullen Taniguchi also fills us in on the basic science side and what was exciting in addition to the Leptin/Symlin combo that we heard a bit about – this was especially exciting, after hearing direct from Dr. Jeffrey Friedman in the DCU #58 interview last month – the Leptin story certainly looks and sounds like it could be even more powerful than we thought and we'll look at that in more depth in an upcoming obesity issue. No time this month – but after taking you on a walk through posters, we will share with you our post-ADA chat with Dr. Jay Skyler, who tells it like he sees it – as does Danish liraglutide PI, Dr. Tina Vilsboll (the full interviews you can download on our website at www.closeconcerns.com).

We'll return to our "DCU Company Watch" next issue, but for now, look for updates on your favorite companies in the ADA download. As for the rest of our issue, following last month's story about our Quince dinner with Dr. Marion Nestle, we bring you a review this month of her recently published and already-bestseller "What To Eat" (some surprises) and a literature review of the NEJM piece she had this month. To boot, we review for you the JDRF's annual meeting – this important organization is on such a roll -- and we preview for you the rest of conference season's big meetings – AADE in August, EASD in September, and IDF in December, in LA, Copenhagen, and Capetown (subscribers can see our customized schedules for you on our website). Won't you join us …?

-- Kelly L. Close

Quotable Quotes from June's DCU:

Dr. Jay Skyler:

- "You know why continuous is really going to win in type 2? When we have factory calibration that can last for a week or so, it will be a whole lot easier to put on a DexCom sensor and leave it in place than it will be to stick your fingers. More importantly, somebody with type 2 diabetes that's been measuring one sugar a week will now have access to continuous glucose monitoring, and they'll be able to look at the impact of what they eat and what it does to their blood sugar. And they'll be able to look at their blood sugars and see, wow, this really is still too high and I have to take something else. And we're going to end up with people who will routinely be walking around with A1c's in the 6's instead of routinely walking around in the 8's and 9's. And that's going to really change the face of diabetes."
- "My therapeutic paradigm over the last year has turned out to be that I start with metformin. If I fail to get adequate glucose control, I add Byetta. If I fail to get adequate fasting control, I add insulin— for most of the year, it's been Lantus, now it's either Lantus or Levemir. And that works for the most part. So I've been very happy with that kind of scheme. I personally stop the SFUs every time I start Byetta; I don't see any compelling reason to continue to give a drug that has weight gain and hypoglycemia associated with it when I can use a therapy that doesn't do those things. I wouldn't see any compelling reason to keep the SFUs on the market once the DPP4s are available.

Dr. Tina Vilsboll:

- "Liraglutide has a beautiful effect on glycemic control and weight loss and it may be used for type 2s very early after diagnosis. Part of the phase 3 research is to determine whether it should be given after diet and exercise, after monotherapy, or later in the course of the disease. A larger indication might result if there are positive effects on the beta cell. "
- "As someone who has been in GLP-1 for a long time, I think it's wonderful that both DPP-4 inhibitors and GLP-1 analogs have come so far. We need to see the phase 3 results of the DPP-4 inhibitors; if they can preserve the beta cell, I could imagine giving a pill to a newly diagnosed patient, and this would be more feasible than an injection. I could foresee a combination with metformin in the early stages of diabetes."

In this issue:

- **Banting Lecture: Harmony and Discord in the Orchestration of Glucose Metabolism, Richard Bergman, Ph.D.**

PART FIVE: Early Stage Science

PART SIX: Post-ADA Conversation with Jay Skyler

2. **2006 Annual JDRF Conference: Global Diabetes Research Forum**
3. **Literature Review: NEJM on Marion Nestle and Food Marketing and Public Policy**
4. **Book Review: *What to Eat*, by Marion Nestle**
5. **Upcoming Conference Preview – *AADE, EASD, and IDF***

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.

- **June 22: Incidence of type 2 intensifies per June '06 *Circulation* and Framingham Heart**
- **June 20: Team type 1 cycles to victory**
- **June 18: Diabetes and the Seattle Mariners**
- **June 16: Stopping the rise in childhood obesity has Arkansas officials smiling**
- **June 14: Amylin and DexCom – Stocks that deserve a closer look**
- **June 13: ADA Day #5 – Parting shots**
- **June 13: ADA Day #4 – Early insulin, pro or con? Emotions run high**
- **June 12: ADA Day #4 – Amylin's just getting started**
- **June 12: ADA Day #4 – Alternate care delivery systems for diabetes**
- **June 12: ADA Day #3 – Postprandial catches up**
- **June 11: ADA Day #3 – Banting Lecture shines**
- **June 11: ADA Day #3 – 11B-HSD hot new target ~ Insulins of note ~ A1c update**
- **June 10: ADA Day #2 – Metabolic syndrome, still controversial, still no agreement**
- **June 9: ADA Day #1 – Abbott shows impressive continuous monitoring data; the floodgates open with the first incretin presentation**

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

1. **ADA Download 2006: Your Guide to Five Days, 15,000 HCPs, 63 symposia, 49 oral sessions, and 1,600 posters**

PART ONE: Our Top Twenty ADA Takeaways

- **#1: Monotherapy is dead, and combination therapy is quickly becoming the standard**. Overall, we believe this trend will expand the diabetes market further. Everywhere we turned we heard "polypharmacy." The doctors we talked to weren't excited about *one* silver bullet . No, they were excited about having all kinds of drugs available to mix and match to improve patients' control.
- **#2: Clinical potential for DPP-4 inhibitors is not so great any way you sliced it (and they tried dozens), but the commercial potential is quite, well, potent, thank you!** A contradiction ? Not really. The A1c reduction isn't that great. The drugs just aren't that potent. Still, consider the competition! While we don't think this is a powerhouse class, it can hit a billion dollars in revenue in a few years. See our incretin story for more on why DPP-4 inhibitors will be a commercial success, why Byetta wins overall, and why Novo's liraglutide comes out smiling.
- **#3: Beta cell regeneration/preservation is the holy grail at the moment, and makers of TZDs, GLP-1, and DPP-4 alike are suggesting that their drugs might prove to reverse the**

disease process of type 2 diabetes. As all studies now are pre-clinical, doctors are cautious, but they say that definitive proof of beta cell preservation or regeneration will move any therapy to the front. The data look promising in animal studies, but more than once we heard that animal data are a far cry from human data. Still the tone seemed cautiously optimistic.

- **#4: Inhaled insulin remains controversial.** With Exubera set to launch in mid July, it was the subject of considerable discussion. Much of it was a version of last year's song: what about lung function? And, this year added a verse. We finally got to touch and feel the Exubera device. It's big. Very big. Many clinicians we heard think it's *too* big to be practical. We are staying tuned on this one. The question, , for us, centers squarely on reimbursement. The very positive upside for us is that inhaled insulin has the potential to lower the population A1c. The downside is that there's nothing novel about the raw material so the reimbursement will be tough, and safety is still an outstanding question.
- **#5: Reimbursement is only increasing in importance as *the* major question of the day**, generally, whether for inhaled insulin, continuous monitoring, or DPP-4s. The managed care companies have incredible power. While it just seems wrong for drugs to be limited when amputations and ESRD aren't, we feel that managed care companies will pretty much do anything in their power not to pay for meds they can avoid. They remind us of the worst of Wall Street – so focused on the short-term. The best of Wall Street focuses on the long-term; couldn't managed care do this too?
- **#6: Weight loss, weight loss, weight loss!** Everybody was talking about weight loss. Byetta was the clear darling but there is also much interest in Acomplia – we think that will die down, relatively speaking, when the drug is approved. But in this market, to become a blockbuster, a drug just doesn't have to be *that* good. And in this age of polypharmacy, we think doctors are salivating at the prospect of having multiple turns at bat to help patients lose weight.
- **#7: Be more aggressive!** We heard a consistent drumbeat on this topic. Consensus? The US is behind the times. One presentation estimated that type 2 patients spend about nine years going more and more out of control until the only option is insulin. We heard many speakers push for much earlier, much more aggressive approaches to get diabetics to lose weight and to get under control.
- **#8: New data on continuous glucose sensing continue to raise the stakes.** Data from both DexCom and Abbott showed higher rates of accuracy. In two oral presentations on the STS, the Pearson correlation coefficient was 0.89 and 0.9, with median MARDs in the neighborhood of 11.4 to 14.8% (mean ARD higher at 15.7 to 19.5%). In a poster, Abbott showed a median ARD of 11.1% and a mean ARD of 14.4%. Patients using either continuous glucose monitor showed an increase in time spent in euglycemia.
- **#9: There is some shifting away from A1c as the exclusive barometer of success, with** more focus on variability, complications' risks, and comorbidites. We heard more than one doctor say that we haven't been paying enough attention to post-prandial glucose. Why now? We think the availability of drugs like Byetta and Symlin finally give doctors a powerful tool that addresses post-prandial excursions.
- **#10: And lest we think episodic has come to a screeching halt - LifeScan's Ultra 2 wins positive notice!** We expect the monitor to do extremely well.
- **#11: CGM has cast new light on A1c.** The original estimates of the correlation between A1c and the average blood glucose value were based on 7-point episodic testing, but a new study by Dr. David Nathan and colleagues has provided more accurate information on the relationship between A1c and average blood glucose. Though more research remains to be done, the preliminary data show that an A1c of 6% reflects an average blood glucose value of 103 mg/dL, whereas the ADA chart currently indicates that it is an average of 135 mg/dL. In contrast, an A1c of 10% really reflects an average glucose value of 251 mg/dL rather than the ADA current of 225 mg/dL. It seems as though the relationship between A1c and blood glucose value may not even be linear!

- **#12: We might be in for some confusion as we get closer to changes in A1c's measurement standards.** During the clinical highlights, the session moderator, Richard Kahn, spoke in quite strident terms about pending gloom and doom as the IFCC gets closer to choosing and implementing a new A1c measurement protocol. One system appears markedly more complicated than the other, which is based on calculating a mean. That said, the overarching goal of harmonizing standards globally is a good thing.
- **#13: Self care was a big focus of the meeting** – are we *finally* getting there!? There were even sessions debating whether self-care is useful (for type 2) and how to integrate it into clinical practice. There seems to be a big push toward patient independence and less inpatient time.
- **#14: The line between pre-diabetes and diabetes is an arbitrary one, and there are increasing questions about when impaired glucose tolerance should be treated.** One question raised was when hyperglycemia becomes diabetes. Diabetes is thought of categorically despite the fact that glycemia is a continuum. A range of hyperglycemia is not considered diabetes in which there is risk for characteristic complications like heart disease, and a question was raised about how the definition of diabetes might affect treatment.
- **#15: Similarly, the concept of the metabolic syndrome was debated endlessly - again**. The metabolic syndrome is a cluster of related symptoms, yet the package does not seem to be any more predictive than the sum of its parts. Speakers and attendees argued about whether the idea of the metabolic syndrome in fact had any practical use. We think it does with patients.
- **#16: Disease cross talk abounded, particularly in terms of diabetes and its** relationship with cardiovascular disease, its relationship to inflammation, its relationship with metabolic syndrome (is there or isn't there one?). We heard a lot about the interconnectedness of diseases. What does this mean? We aren't exactly sure but we wouldn't be surprised to see some creative, nontraditional uses of drugs to help diabetics avoid complications
- **#17: The difficulty of coming to a consensus about the best treatment, despite evidence, came through strongly**. The variety of patient populations within the US, not to mention globally, is huge. The debate over early insulin treatment in type 2 patients especially brought out this challenge.. With somewhat equivocal data concerning the comparison of early insulin treatment to later treatment (hopefully, the ORIGIN trial expected to come out in 2008 will help), the early use of insulin was a byproduct of income level, education (one HCP said many of her patients could not count), hospital resources, and access to diabetes education..**[.**
- **#18: The earlier-stage science was fascinating, as researchers are exploring new drugs. .** Of particular note were Dr. Thomas Mandrup-Poulsen's lecture on the potential for treating type 2 diabetes with an IL-1 receptor agonist and Dr. Jonathan Seckl's review of the regulation of cortisol, a "stress hormone" that increases blood sugar levels, via the enzyme 11B-HSD1.
- **#19: There are new understandings, and with them new questions, about the mechanism of the disease**. In particular, free fatty acids and inflammation appear to play a role in beta-cell function. There was disagreement as to what role they played in the decline of beta-cell function. On one hand, many think lipotoxicity increases glucotoxicity in beta-cells, and on the other, fatty rats seemed to show isletogenesis, or the production or growth of beta-cells due to free fatty acids. **Inflammation is implicated, again.** Every time we turned around people we consider smart and forward thinking were talking about inflammation as a clear culprit in diabetes.
- **#20**: **Tight glucose control in the hospital setting continues to heat up. Dr. Bruce Bode nailed it, in our view: "A blood glucose > 200 mg/dL in the hospital patient causes increased morbidity and mortality. In the 21st century, blood glucose >200 mg/dL in the hospital will be considered malpractice…"** We continue to watch JCAHO. And can the hospitals save the insulin manufacturers? The manufactures are certainly more focused than they were a year ago, which bodes well for small companies pursuing tight glycemic control in the hospital. Lilly has Byetta, yes, and Novo has liraglutide, but they, and Sanofi, still need to work on the insulin franchises, now more than ever. Can Insulet be part of the magic "teachable moment" as patients that leave the hospital learn insulin? Seems so, and we're staying tuned…

PART TWO: Synthesis by topic of presentations, posters, symposia, oral abstracts, and exhibit hall

THE INCRETIN FRENZY: A Summary

For the uninitiated, the Friday night symposium was the first clue.

The scene outside of the Novartis-sponsored symposium, "The clinical impact of incretin-based therapies on type 2 diabetes management," held at Washington's tony Grand Hyatt, bordered on hysterical—the crowd began arriving an hour in advance, and when denied admittance to the lower-level symposia hall until 7 pm sharp, hundreds of people crowded around the down escalator, jostling for a place in line. The line overflowed into a cocktail party taking place on the mezzanine level and continued two floors up. When the line finally advanced, many were left outside. We saw one man cry. Others tried to sneak past those guarding the door. It was not civilized, and more than one comparison to a rock concert was made. *Diabetes Close Up* snagged one of the very last seats in the room (we pre-registered), which was packed with close to 1,000 people.

Expectations have reached a frenzy.

On one level, the hysteria was understandable. The CDE seated to our left, herself a patient with type 2, had lost 41 pounds on Byetta and had stopped taking insulin (Lantus). We suspect that we could have sat down at any table and heard similar testimonials, as tales of weight loss were running wild during our five days in DC.

This specter of sveltness has translated directly into consistent sales. We peg the combined market for Byetta/LAR (LAR is the weekly injectable that we believe will be available in 2008) looks to us to be $5 billion-plus, and that assumes a very low 15% penetration ($2,750/year/price * 15% of type 2 patients = $6.1 billion). Could it be bigger? Of course! We smiled at a *New York Times* headline the other day about the drug – Byetta, a billion dollar drug? Is there any question? At present, for us, the question is more about whether it'll be single or double digit billions.

Another question now centers on two other incretin therapies on the brink of approval. How many type 2 patients will go on glucagon-like-peptide-1 (GLP-1) agonists (which increase insulin secretion) and/or dipeptidyl peptidase 4 (DPP-4) inhibitors (an enzyme that rapidly degrades GLP-1)?

Here's the downside on the DPP-4 inhibitor front: the drugs just aren't that potent. The A1c reductions aren't that significant. We're fairly unimpressed with the class clinically and generally think poor reimbursement will hurt it in the early days (and likely the later days). Whereas 70% of covered lives in the US are said to be at tier 2 or better status, we doubt the DPP-4 inhibitors will see such success. Nonetheless, we're positive on *both* GLP-1 and DPP-4 inhibitors in terms of their commercial potential. With just under 15 million diagnosed patients with diabetes in the US, most of whom are doing poorly, and with an expected increase of about one million patients each year, even a mediocre drug (one that results in an A1c drop of roughly 0.60%) can be a blockbuster.

For example, we think despite the fact that DPP-4 inhibitors don't represent a powerhouse class, the class can easily hit a billion dollars in revenue in a few years. Why the optimism? If you put all the sales of all the anti-diabetic drugs together, it's close to $15 billion dollars. And when you think about it, all of the established drugs have fairly substantial defects.

- TZDs, a $4 billion class, have issues (weight gain, edema, congestive heart failure)

- Metformin, a billion-dollar-plus drug before going generic, has issues (53% of patients in the treated group (n=141) of a placebo-controlled study experienced diarrhea and 26% experienced nausea, compared to 12% and 8% of the placebo group. The most common side effects with metformin are nausea, vomiting, gas, bloating, diarrhea, and loss of appetite; these symptoms occur in one out of every three patients).
- Insulin – oh let's not even start! Okay, insulin has issues: Many patients associate it with failure; it has to be injected; it often prompts hypoglycemia; taking it requires complicated dosing regimes – oh, and it prompts weight gain.

So, with spiraling patient numbers and growing pressure to treat people early and aggressively, we believe the drug market can support all comers for some time. Generally, we think doctors may prescribe DPP-4 inhibitors early, as an add-on therapy to metformin, though we don't think the product's emergence will slow down Byetta and we also don't really see it being used as monotherapy. Metformin is the monotherapy gold standard – cheap and potent (arguably tolerable and arguably not, see below).

Will GLP-1 and DPP-4 inhibitors be synergistic? Perhaps, although we don't foresee wide combination use of *those* two due to cost. But metformin and Byetta? Check. Metformin and DPP-4 inhibitors? Check. Byetta and TZDs? Check (Dr. Bernie Zinman oral commentary was really quite persuasive). TZDs and DPP-4 inhibitors? Maybe. Byetta and insulin? Check. Insulin and DPP-4s? Maybe, for skinny type 2s (all nine of them).

Lest there be any question (and amazingly, there does appear to be), let us note our humble view that there is room for both GLP-1 and DPP-4. Anyone who is educated and can benefit from weight loss may go straight to Byetta, or liraglutide once it's approved, but doctors, especially primary care doctors, may go for DPP-4 first since it's easier to give and take, if not as potent. Much will hinge on reimbursement. If there is not good reimbursement for DPP-4 inhibitors as first-line therapy, and we doubt there will be, we believe it will take a lot longer for PCPs to prescribe this class. Reimbursement is already quite good for Byetta and only getting better – fully 70% of covered lives have Byetta as a Tier 2 option on the formularies. (One of our takeaways from ADA was actually that despite reimbursement being good, there's actually still room for it to get better.) Reimbursement for DPP-4 inhibitors will be much slower, especially as monotherapy, and whether the entry of DPP-4 inhibitors will influence Byetta, overall, we think it will be minor: rather, we expect the whole diabetes pie to grow

In short, more alternatives coming to a market that has ever so badly needed alternatives can only be good. We see metformin continuing to hold as a solid first-line drug, and we're medium bullish on the Merck drug that combines DPP-4 inhibitor Januvia with metformin, depending on reimbursement. More than ever, once we're past this supply blip, we will see patients continue to go on Byetta at every stage of the disease. Ultimately, so many will be going on more aggressively therapy earlier that prandial insulin will continue to grow as a class – but not as much as it would have! Below we synthesize our research on incretins from ADA 2006.

DPP-4s, boasting high "tolerability profile," are coming close to market

As noted, we've been a bit underwhelmed by the prospect of DPP-4 inhibitors, but we sensed at ADA a real undercurrent of excitement about these investigational oral agents; specifically, Merck's sitagliptin (Januvia) and Novartis's vildagliptin (Galvus).

Sitagliptin was accepted for FDA review February 15, and we expect FDA action by mid-October. Sitagliptin has been proposed for once-daily administration of a 100 mg dose. In a 24-week monotherapy study (1995-PO) presented at ADA, sitagliptin lowered A1c by 0.79% (placebo-subtracted) from a baseline of 8.0%. We suspect that the baseline rose during the drug washout period of unspecified length

that occurred between measuring of baseline A1c and initiation of therapy, so this is actually less impressive than it might sound. In a 12-week Japanese study, the placebo-subtracted A1c drop was a full percentage point, but we note that the A1c in the placebo group climbed about 0.4% (537-P), so the "real" drop was closer to 0.6%.

Vildagliptin also has an FDA action date in Q4 2006. In a 24-week study in which 100 mg vildagliptin was given twice daily—which, of course, makes it difficult to compare to the once-daily sitagliptin studies—A1c dropped 0.9% from a mean baseline of 8.4%. The effect increased with a higher A1c baseline, so that among patients who had a baseline of 9.9%, the A1c drop was 1.7%. Studies have shown both vildagliptin and sitagliptin to be weight neutral. There was one that caused early excitement because vildagliptin actually looked like it prompted weight loss, but in that study, even the placebo group lost weight – *all* in the trial did, since instruction on weight was, um, part of it. We don't believe DPP-4 inhibitors actually prompt anything but weight neutrality, as the weight loss seen with other GLP-1 agents is thought to be related to the pharmacological levels of GLP-1; DPP-4 inhibitors preserve lower, endogenous levels of the hormone. Although they do not cause weight loss, weight neutrality in the landscape of diabetes treatments has heretofore actually been rare and valued as an advantage over sulfonylureas, TZDs, and insulin. This has begun to change with Byetta, and we'll continue to monitor how.

We don't expect the DPP-4s to be used in monotherapy – metformin is just too good, too cheap, and too safe to change it, except in people who cannot tolerate it. While vildagliptin bested rosiglitazone (GSK's Avandia) results in a head-to-head study, it failed non-inferiority to metformin. (Data presented by Dr. Sylvia Dejager at ADA showed a 1.0% drop in A1c with vildagliptin versus a 1.4% drop with metformin; this drop was statistically significant, 120-OR.) Both Merck and Novartis have more impressive studies of their respective DPP-4 inhibitors in combination use. As an add-on to metformin, vildagliptin lowered A1c by 0.9% from a baseline of 8.4% over 24 weeks; in that study, A1c in the placebo plus metformin group rose 0.2% (121-OR). Sitagliptin shows a similar effect when added to metformin, with a drop of 0.65% from a baseline near 8%.

Late-breaking data released Tuesday morning at ADA showed that vildagliptin in combination with TZD (Takeda's pioglitazone) lowered A1c by 1.9% over 24 weeks from a baseline of 8.7%. This was statistically significant when compared to the change in A1c for those on pioglitazone alone (1.4%, $p<0.001$). In that study, 65% of the patients in the treatment group achieved an A1c of under 7%, and there was less weight gain and less peripheral edema than seen with the TZD alone (though more than with vildagliptin alone). In Merck's add-on to pioglitazone study, the difference in A1c versus placebo was -0.70%, from a baseline of near 8%, and just 45% of the treatment group achieved an A1c under 7%.

Most notably, both drug makers emphasize the clean tolerability profile of the DPP-4 inhibitors: rare hypoglycemia, no weight gain, no edema. This tolerability profile appears to be a highly valued point among doctors, particularly primary care doctors, who want simple solutions for their patients that will generate fewer phone calls. Focusing on it is smart. And these drug makers are deft – they are good at making an imaginary link associating tolerability with safety – we watch, ruefully, and shake our heads. Although many experts seem less worried about safety, we still stand by our view that no one can really explain how these drugs work, and no one can really talk at any length about what else may or may not be being inhibited. Alas – this doesn't mean they won't be commercially successful.

Over time, we believe as others do that the DPP-4s will phase out sulfonylureas; Merck, for example, has shown non-inferiority versus the SFU glipizide as an addition to metformin over 52 weeks. In that head-to-head, patients on sitagliptin experienced dramatically fewer hypoglycemic events (4.9% versus 32%, $p<0.001$), and patients in both groups experienced an A1c drop of 0.7%. The difference in body weight change between the two groups over the course of the year was 2.5 kg, or 5.5 lbs.

So are these two drugs, sitagliptin and vildagliptin, even different? Of course, first of all, it's hard to really compare them since the trial designs vary, etc. Actually, as it turns out, there do appear to be subtle differences. Sitagliptin appears to be a more powerful inhibitor: at the end of 24 hours, sitagliptin might still be at 70% strength compared to only 45% of DPP-4 inhibition still active with vildagliptin. However, according to incretin expert Dr. Daniel Drucker, this does not necessarily mean that sitagliptin is better. The two drugs do not appear to differ during the day, only perhaps during the night, when the strength is not as important. On the flip side of this, Novartis states that there are no anticipated dose adjustments for special populations with vildagliptin whereas those with renal issues will need different dosing with sitagliptin. (A 2003 survey estimated that 13% of adults with type 2 diabetes had chronic kidney disease, equivalent to over 1 million people.[1]) Merck anticipates that for moderate to severe renal failure patients, dosing would be lowered to 25-50mg.

A key difference may be that sitagliptin will be given once daily, whereas it is not yet clear whether vildagliptin will be once daily or twice daily. Novartis has applied for a once daily approval, but studies were done with both once-daily 50 mg and twice-daily 50 mg administration. If vildagliptin is recommended for twice-daily dosing, it may or may not be an actual disadvantage, especially if taken in combination with another drug; both metformin and TZDs require twice daily dosing. Perception, however, will favor the once-daily drug.

New trials into the effects of DPP-4 inhibition may give additional insight into their secondary effects. At ADA, data presented by Matikainen and colleagues showed that vildagliptin decreases postprandial triglyceride levels, thus potentially reducing the risk of macrovascular and microvascular complications. Vildagliptin also was found to restore acute insulin response to glucose (AIRg) in drug-naïve type 2 diabetic patients (D'Alessio D, et al) and to reduce blood pressure levels in type 2 diabetic patients (Nathwani A, et al.).

Liraglutide is primed to compete with Byetta, though not LAR

Novo Nordisk released late-breaking data on its phase 3 incretin compound, liraglutide. A GLP-1 agonist, liraglutide functions in a manner similar to Byetta in that it activates the GLP-1 receptor. Unlike Byetta, liraglutide is a modified human peptide and shares a 97% homology (similarity in the amino acid sequence of the protein) with GLP-1, compared to Byetta, which has only a 53% homology. To enable slow release, liraglutide is bound to a larger protein known as albumin, from which it gradually dissociates and diffuses into the body. Possibly due to this increased homology, antibodies have not been seen with liraglutide injection that are seen with exenatide injection, though it is not thought that these antibodies have any clinical significance. We also note the possibility that "zero" antibodies reflect a less sensitive titer.

In clinical trials, liraglutide showed a 3 kg weight loss and a 1.7% difference in A1c compared to the placebo group after 14 weeks from a starting, post-washout A1c of 8.1-8.5%. Importantly,, we note that pre-washout, A1c's were 8.0 – 8.2%, so the pre-washout-comparison drop is about 1.4 points. Triglycerides were reduced on average by 30%, and markers of inflammation like PAI-1 and BNP were reduced by 35% and 38% respectively in the high dose group compared to placebo. Markers of inflammation received more attention of note at this meeting than we've noticed before.

According to Dr. Tina Vilsboll, a full-time clinician at the Steno Diabetes Center in Denmark who has conducted clinical trials using liraglutide and who presented the data, liraglutide appears to have a greater effect than on fasting blood glucose than might have been expected (see our website

[1] JAMA 2003;289:3273-3277

www.closeconcerns.com for our full interview with her!). Dr. Vilsboll told us that, in her studies, there was a fasting effect of more than 3 mmol/L (54 mg/dL). She stressed that Byetta and liraglutide should not be examined side by side because there have not been comparable trials and she herself has not studied Byetta. She did conjecture, however, that this effect on fasting glucose might be explained by insulin's active profile. "*Byetta appears to have a peak after injection, and liraglutide has a profile more like Levemir*." Given its flatter curve, it is not clear whether the magnitude of liraglutide's effect on post-prandial glucose is equivalent to that of Byetta. In studies, the post-prandial effect has been greater than placebo; although no head-to-head study of liraglutide versus exenatide has been completed, liraglutide's post-prandial effect looks to be not as great. The main adverse events in the high-dose liraglutide group was diarrhea (19.5%) compared to placebo (12.5%); these events waned over time. In the high-dose group, 10% of the subjects experienced nausea.

Dr. Vilsboll said that the indication for liraglutide may depend on the results of the phase 3 studies. "*Liraglutide has a beautiful effect on glycemic control and weight loss*," Dr. Vilsboll said, "*and it may be used for type 2s very early after diagnosis. Part of the phase 3 research is to determine whether it should be given after diet, after monotherapy, or later in the course of disease. A larger indication might result if there are positive effects on the beta cell.*"

Though liraglutide may be an alternative for patients interested in GLP-1 injectible therapy, it won't be available until 2008, near the expected launch of Byetta LAR. Assuming all goes as expected with LAR, we expect patients and doctors to flock to the weekly injection, and we would look for at least 40-50% to convert from Byetta during the first year of LAR (and perhaps 80% over three years – again, no rush). Reimbursement, availability, and inability of some to tolerate LAR vs. Byetta would keep conversion more limited at the start, but we would imagine that any patient ultimately interested in LAR would start with Byetta, perhaps making any other GLP-1 dead in the water.

Novo is undoubtedly working on its own long-acting version, but for now, liraglutide is anticipated to be competitive only with Byetta "classic." Since we imagine them hitting the market at roughly the same time, c. 2008-09, we're not sure how competitive liraglutide actually would be, although we do see the one vs. two injections per day as favorable. We look forward to Phase 3 data, which we would expect to see at next year's ADA, and perhaps even some at IDF in December. So exciting! Currently, we estimate that Byetta has penetrated *well* less than 2% of the available market – yes, there's significant upside!

Byetta is still the main attraction

When a drug company has to plead with doctors to stop prescribing to new patients because demand is outpacing supply, as happened with Amylin last week, it's obvious that the drug has taken off. This is a positive for patients and for doctors, because it reinforces what we already knew – Byetta works, works really well, and has the capability to help far more patients. The timing of ADA for Amylin must be something of a mixed blessing, as the enormous exposure hits right as they work to ease demand, and we can only predict that Byetta's unintentional hard-to-get status (one sure way to make people want something is to tell them they can't have it) will drive doctors and patients, well, crazy.
Amylin released late-breaking data at ADA and took the conference by storm with two Byetta-related oral presentations, two symposia, and eight posters (not to mention the Byetta-plastered buses and Byetta bags, which were hardly needed, but fun). The key new data were Byetta's use in combination with TZDs, which was presented by Dr. Bernie Zinman; data from the Byetta extension study; and results of a study of Byetta LAR. More so than the data were just the stories, as most of the doctors we talked to had one to tell.

But the data are pretty good. The study of Byetta in combination with TZD (117-OR) included 233 subjects failing TZD and metformin; at 16 weeks, the subjects receiving Byetta rather than placebo saw a

decrease of 0.8% in A1c from a relatively low baseline of 7.9% and a reduction in body weight of 1.5 kg (3.3 lbs.). Sixty-two percent of subjects in the exenatide group had an A1c below 7.0 at trial end, versus 16% in the placebo group.

Results of a 45-person trial of exenatide LAR were finally released at ADA (487-P), assessing the effect of exenatide LAR as an add-on to metformin or diet and exercise. Kim et al. reported that patients receiving 2.0 mg of exenatide LAR showed a 2% improvement in A1c and 8.4 pound weight loss over 15 weeks, "*with no evidence of plateau*." Eighty-six percent – 86%! – of patients achieved an A1c below 7% (strangely, in the liraglutide trial, less than 50% got to a goal of less than 7 A1c). Twenty-seven percent of subjects in the 2.0 mg group experienced nausea, compared to 15% in the placebo group. Although we do not have detailed safety data, the investigators reported that there were no adverse events leading to early withdrawal from the study. Also keep in mind, the patient population was so small that 1 patient equated to a 6-7% change in adverse event statistics, so that isn't particularly meaningful. Notably, the A1c drop was better, the tolerability was better, and the weight loss was better than was seen in the AMIGO trials. We believe that because patients always have drug on board with LAR, the effect is more physiologic. In our view, this attribute is why patients appear to do better with this formulation than seen in earlier trials for Byetta. Anecdotally, we have reported that patients with "real world" use fare better than did those in trials – how excellent is that?

But there is more. The Byetta extension study reported at ADA (485-P) showed sustained improvements in A1c and no plateau on the weight loss out to two years. In the study, 283 patients on twice-daily exenatide saw an A1c reduction from baseline of 1.1% at two years, which was the same as the reduction at the end of the initial 30-week trial. The average five pound weight loss seen at 30 weeks increased to 10 pounds at two years. The sustained weight loss led to one question of whether doctors were "*concerned that the weight loss didn't stop*" (the doctor wasn't concerned, and we assume the weight loss could continue like that for several years with no concern that patients would drop below their ideal body weight). We also listened for news on Amylin's three-year open label data – there, a full point A1c reduction was still seen, and the weight-loss continues – the rate is slowing but the curve remains pointed down. We wonder whether three-year improvement is enough to assume some sort of beta cell protection – perhaps too early to tell, but we will certainly continue to watch.

In a study conducted by Davis and colleagues (456-P), 62% of type 2 diabetic patients were able to maintain glycemic control after substituting exenatide for insulin, while glycemic control deteriorated in the other 38% of patients. Thus, as we have suspected, substituting exenatide for insulin may be feasible for some type 2 diabetic patients although at present, such use is clearly off-label.

DPP-4 vs. exenatide face-off comes out mixed

Some doctors disagree over how patients respond to injectables. Exenatide and other injectible GLP-1 analogs offer the benefit of weight loss balanced by the minus of injection, but just how patients and doctors weigh these two factors is not yet clear. At ADA, Dr. Andrew Drexler told us that he would support the use of Byetta prior to DPP-4 inhibitors following their approval: "*In my experience, people don't seem to mind the injections because of the weight loss. Byetta is easy: it isn't insulin, it won't cause hypoglycemia, and dosing is simple. People will tolerate a lot for weight loss.*" Indeed, many doctors seem to say the same thing: their patients love Byetta, and they don't mind injections.
On the other hand, noted GLP-1 expert Dr. Dan Drucker said, "*I disagree with all these people who say there is no resistance to injections. Most people prefer a pill. Injections will be later in the game unless there is once-weekly dosing with LAR.*" Dr. Drucker said that he will start with metformin and a DPP-4 inhibitor and then will add on a TZD. The weight loss that is seen with GLP-1 but not DPP-4 inhibitors is due to the greatly elevated, pharmacological levels of GLP-1 present in the injectible, but it also appears to be these greater levels that lead to nausea that is not seen with DPP-4 inhibitors.

While the tolerability of DPP-4 is impressive, as noted, questions remain about safety. In a presentation at a Novartis-sponsored symposium on incretin-based therapies , Dr. Drucker said that DPP-4 also mediates immune function, where it is known as CD26; it is not yet clear whether selective inhibition will influence intracellular signaling of lymphocytes. DPP-4 plays a role in inflammation; DPP-4 knockout mice are more prone to autoimmune arthritis and have defective immunoglobulin secretion in response to immunization. Although this shows that mice with no DPP-4 action at all have immune- and inflammation-related problems, DPP-4 inhibition in humans is a different story, and it is not clear that there will be similar problems. To date, DPP-4 appears safe, and whereas at last year's ADA, doctors appeared quite concerned about what else DPP-4 inhibitors were inhibiting, this year they seem more sanguine. We suspect we will not know whether there are problems until it is approved and available in larger populations. A panel meeting would provide useful fodder – we look forward to having many experts gather 'round a table' to discuss these issues.

Beta cell preservation or regeneration would be golden ticket

One point on which there is absolute agreement is that any therapy that can halt or reverse the decline in beta cell function and mass will rise to the top. In debating the merits of DPP-4 inhibitors versus GLP-1 agonists, Novo investigator Dr. Tina Vilsboll, said, "*We need to know if it's true that DPP-4 inhibitors preserve the beta cell. If they can, I could imagine giving a pill at a very early stage. This would be more feasible than telling someone to inject themselves. But we need to look at the effect on the beta cells; it is better to give the analog sooner if it does have a preserving effect on the beta cell*." Dr. Andrew Drexler echoed the popular sentiment when he told us that "*any therapy that preserves beta cell function should be front line*."

As noted by Dr. Barry Goldstein of Thomas Jefferson University, there is an important distinction between a therapy that increases beta cell function—that is, increases insulin production of each individual cell—and one that improves or maintains the number of living beta cells. Existing diabetes therapies such as sulfonylureas can increase insulin production for a period of time, but in our vast armamentarium, no current therapy can reverse the steady decline in beta cell function and mass. Further, it's thought that SFUs actually wear down the beta cells - another fear associated with this increasingly unpopular class.

Both GLP-1 agonists and DPP-4 inhibitors have shown expansion of beta cells in mice in pre-clinical (animal) studies. Immediately prior to ADA, for example, data published in *Diabetes* by Mu and colleagues showed beta cell preservation in mice treated with sitagliptin.[2] Similar studies have been done with exenatide.

In humans, however, there are no simple ways to measure beta cell preservation or regeneration. The HOMA test (Homeostasis Model Assessment) provides an estimate of beta cell function but is not considered to be appropriate for a prospective study of beta cell life. In general, HOMA tests, C-peptide levels, and fasting proinsulin/insulin ratios are thought to give insight into the amount of insulin secretion, which is not necessarily correlated with beta cell mass. In humans, sitagliptin increases HOMA-Beta and decreases fasting proinsulin/insulin ratios. Likewise, vildagliptin shows "*nearly a five-fold increase in beta cell function*" as well as improved first-phase insulin response, but whether there are long-term salutary effects on the ailing beta cells is not yet known. Also reported at ADA (522-P), Mari et al. found that the once-daily GLP-1 analog liraglutide enhances measures of beta cell function.

[2] Mu J, et al. "Chronic Inhibition of Dipeptidyl Peptidase-4 With a Sitagliptin Analog Preserves Pancreatic β-Cell Mass and Function in a Rodent Model of Type 2 Diabetes." *Diabetes*. June 2006. 55: 1695-1704.

"The data are very strong in rodents for both liraglutide and exenatide; increased proliferation and decreased apoptosis have both been seen, but it's still an open question with respect to human beta cells," Dr. Vilsboll said. "You need to evaluate differences in beta cell function a number of months after the medication has been stopped."

The incretin crowd is not the only one clued into the value of a long-term disease modification; the ongoing ADOPT and DREAM trials will assess whether TZDs might modify the course of disease as well. When similar long-term data are available for GLP-1 agonists and DPP-4s, we believe this will be the differentiating factor in providers' choice of 'scripts. Novartis announced at ADA that it will be backing a mega-trial called GLORIOUS, described as "*one of the largest series of outcomes-focused clinical programs conducted among people with type 2 diabetes.*" More information on GLORIOUS is expected to be available in the second half of this year. In the meantime, we wait for DREAM and ADOPT and believe that positive studies will be positive for the incretin class.

Conclusion

We think that to date fewer than 200,000 patients receive incretin therapy – about 5-10 million fewer than we believe could benefit. If we are right, this class has barely crossed the starting line. It's clear from our writings that we like some drugs better than others, but we believe all could have a place, and we do not believe that any one drug will be a silver bullet. Rather, doctors are going to have multiple combinations from which to choose, creating therapeutic alternatives for patients and financial opportunities for drug companies.

Breaking Down the Inhaled Insulin Debate

People love to *talk* about inhaled insulin. After years of anticipating this miracle drug, ADA attendees still perk up their ears when inhaled insulin is mentioned. Crowds flooded inhaled insulin sessions, throngs of attendees surrounded the Exubera booth, and inhaled insulin posters were some of the most popular . What's all the fuss? Depending on whom you ask, inhaled insulin is a next big thing or it's old news. Let's break down the debate.

Julio Rosenstock, director of the Dallas Diabetes and Endocrine Center, was the pro-Exubera gladiator at ADA, giving talks left and right about its successes. Dr. Rosenstock presented his oral abstract "Inhaled human insulin (Exubera) therapy shows sustained efficacy and is well tolerated over a 2-year period in patients with type 2 diabetes." Following his well-received presentation, Dr. Lois Jovanovic gave a very similar talk about Exubera in type 1 patients.

When he spoke, Dr. Rosenstock began by mentioning a previous study that showed Exubera to be as efficacious as subcutaneous (SC) injection but to have small differences in lung function as measured by pulmonary function testing (PFT). In his oral abstract, Dr. Rosenstock presented new data from a two-year, multi-center study again comparing Exubera and SC injection but this time with a highly standardized pulmonary function test (PFT) design. PFT measures included forced expiratory volume in one second (FEV1) and carbon monoxide diffusing capacity (DLco). Both groups, Exubera and SC injection, had a mean A1c drop from 8.0% to 7.3% sustained over two years. Exubera offered a much more significant drop in fasting plasma glucose (FPG) than SC injection, a difference that could not be accounted for by differences in basal insulin intake. Both groups caused hypoglycemia to drop over time. =Finally, Exubera demonstrated less weight gain when compared with SC injection in both type 1 and type 2 patients. These results certainly made Exubera look like an attractive alternative to SC injections.

At a CME dinner symposium presented by Pfizer, Dr. Rosenstock continued to speak on the promise of inhaled insulin. He presented a study showing that inhaled insulin combined with oral agents brought

A1c down from 9.2% to 7.3%, while inhaled insulin treatment alone brought it down from 9.3% to 7.9% and oral agents alone brought it down from 9.3% to 9.1%.

The finding that generated the most questions from both the type 1 and type 2 presentations was an unexplained peak in antibodies. Insulin antibodies peak at 6-9 months for type 2 and at 12 months for type 1 after the start of treatment. Researchers do not yet understand why this occurs and it will require significant future research. Pro-Exubera doctors seemed to brush this finding under the rug though, repeating that the insulin antibody peak is not correlated with dosage, glycemic control, or biovariability.

Exubera's biggest concern is pulmonary problems. An early dip in both FEV1 and DLco was exhibited with Exubera; even though the change was small, it occurred in the very beginning of treatment and was non-progressive. A cough occurred in 38.9% of patients on Exubera and 14.1% patients using SC injections. According to the researchers, the cough is mild.

Dr. Klaus Rave presented an oral abstract titled "Pharmacokinetics (PK) and glucodynamics of human insulin inhalation powder (HIIP) in subjects with chronic obstructive pulmonary disorder (COPD)." Dr. Rave looked at Air Insulin (human insulin inhalation powder) in patients with COPD, specifically chronic bronchitis and emphysema. His results showed that Air Insulin was significantly more effective in healthy patients than in COPD patients. A major cause for concerns was the significant FEV decreases in COPD patients when using Air Insulin. Due to these findings, the researchers advised further research in this area and recommended not using inhaled insulin on those with COPD.

At a lunch with Dr. Drexler and Dr. Barry Goldstein, Dr. Drexler spoke about the competition between Exubera and Byetta over post-prandial glucose – he says it's clear Byetta is going to win.

Dr. Drexler thinks Exubera is too late – it might sell well for three months because of the novelty of inhaled insulin but after that the inconvenience of the device will drag down sales. He does not believe that the device is subtle enough. People will not take the Exubera "briefcase" into a restaurant, much less use it at the table. Also, Byetta works great and people lose weight. The weight loss and appetite suppression of Byetta are such huge benefits and are not to be underestimated . With that said, he's not totally down on inhaled insulin. He's doing work for Mannkind, but that technology is at least two years away, probably three.

Dr. Goldstein agreed with Dr. Drexler about the inconvenience of the Exubera device. He's concerned that patients are expecting an inhaler-like device – and why would a payer reimburse for something that is likely to "end up in a drawer." Dr. Goldstein noted however that the Exubera booth in the exhibit hall was packed – "with financial people." (You know who you are.)

Bottom line – when the main selling point for a product is an improved patient acceptance, a cumbersome device doesn't help.

Asked whether Exubera would have to have additional advantages—apart from its mode of delivery—over Byetta, the doctors said that no, form factor is important. One went so far as to call the device itself "a dinosaur." If inhaled insulin could be as discreet, say, as an asthma inhaler, it may very well be successful. Dr. Goldstein mentioned pens, saying that Europeans have them because they are "smarter."

A major concern with Exubera is that the long-term effects are still unknown. Dr. Goldstein seemed dubious, and he said that there are changes in lung function, though they appear to be stable, but he questioned why anyone would take the chance of using the drug when the long-term effects are unknown. He said that he does not believe there is a large number of people who refuse injection but will jump at

the opportunity to inhale insulin, or at least that this number is not as high as Pfizer is predicting. Drexler also noted that the inhaler for MannKind is smaller and may be more viable (see above).

Insulin as Initial Treatment? Emotions Run High

Before incretins, it seemed obvious that far more patients need to go on insulin, as evidenced by the poor outcomes - as most who follow diabetes know very well, roughly two thirds of patients are considered to be "out of control." In fact, we believe this estimate is likely on the very low side. So in the "early insulin - yes or no" session, the Q&A period of the debate revealed the variety of patient populations worldwide and the difficulty in standardizing a treatment. The subject of insulin as an initial treatment continues to be quite controversial, so there was good turnout at the session, a lot of participation, and emotions ran quite high.

Dr. **Jaime**Alvarsson claimed insulin was easier to intensify once patients were on it, that it might eliminate glucotoxic effects on beta-cells, and that, by the results of his own study, a patient's quality of life does not appear to be affected by treatment (only complications). In contrast, D**r. Jaime**Davidson claimed that early insulin treatment is unnecessary if we can attain glycemic control since his experience shows that a patient's lifestyle changes very much when he or she is put on insulin and that patients often fail to adequately consult with health care providers after insulin treatment begins.

The issue of diabetes education was therefore big. Insulin treatment is difficult when patients are under-educated and under-supported. While Dr. Davidson suggested that step treatment could avoid having to teach a patient SMBG, Dr. Irl Hirsch made the comment, to a flurry of applause, that they need to learn SMBG whether they are going on insulin or not! We know that information prompts engagement, and that patients need to know where they are to figure out where they are going. The idea that SMBG can be skipped is absurd to us. Even if patients aren't on insulin, SMBG can still be quite helpful in figuring out the impact of various foods, the glycemic index of these foods, the impact of exercise, etc.

Dr. Rosenstock, Director of the Dallas Diabetes and Endocrine Center, also spoke on the promise of early insulin. Early insulin treatment may save beta-cell function as it allows them to rest during insulin resistance. The Origin Trial studying the effects of early insulin treatment in humans should be ready by 2008. Out of 12,000 patients, half will be on standard step-therapy and treated to target A1c of <7%, and the other half will be on basal insulin (glargine) with a target blood glucose level of <95 mg/dl. The trial may provide strong evidence for insulin as a front-line treatment.

Switching gears, new developments in basic science are breaking down the barriers of insulin resistance. In his presentation titled "11B-HSD1: The role in insulin sensitivity and obesity," Dr. Jonathon Seckl discussed the work that is being done to pursue 11B-HSD1 as a hot new drug target for the treatment of obesity and metabolic syndrome. Cortisol, known commonly as the stress hormone, is a corticosteroid hormone that is involved in a stress response. Cortisol is thought to contribute to visceral obesity and insulin resistance, and elevated levels of cortisol are typical in metabolic syndrome. In the body, an enzyme known as 11B-hydroxysteroid dehydryogenase (11B-HSD1) shuttles cortisol between active and inactive forms (cortisone). A high-fat diet upregulates this enzyme, and people who are overweight or obese make more cortisol in their fat tissue, paradoxically. A mouse made to overexpress 11B-HSD1 showed hyperphasia, increased insulin resistance, and obesity.

Knockout mice, or mice that have no receptors for this enzyme, show improved glucose tolerance, lower triglycerides, higher HDL, and do not become insulin resistant even with high fat feeding. Their levels of leptin, resistin, and TNF alpha drop. Dr. Seckl listed Biovitrum and AmGen as companies doing work on inhibiting this enzyme. Biovitrum is doing work with arylsulfonamidothiazoles (ASTs), which selectively inhibit the enzyme. Licorice is a natural substance (carbenoxolone) that inhibits both HSDs and improves

insulin sensitivity. Dr. Seckl noted that the enzyme is important in inflammatory processes, and resolution of arthritis is delayed in knockout mice. Inflammation is a potential problem that could result from the inhibition of this enzyme.

Much conversation at the ADA focused on better mimicking a "normal" body's physiology, the importance of improving glycemic control, and the need to pay more attention to post-prandial excursions. To that end, we were intrigued by the oral poster presentation on a new very rapid acting insulin formulation. We see lots of promise for better control, use in a pump, and as an enabler for an artificial pancreas. We were also lucky enough to speak with Dr. Wendell Cheatham on the topic of very rapid acting insulin.

The insulin delivery oral presentation that we found the most exciting was "Pharmacodynamic Properties of Viaject: A Novel Rapid-Acting Regular Human Insulin," presented by Dr. Solomon S. Steiner. The aim of this study was to evaluate pharmacodynamic properties of a product called Viaject compared with Humulin and Humalog lispro. Viaject is a formulation of regular human insulin and GRAS (Generic Resource Allocations Strategies) **I**ngredients designed to increase the rate of insulin absorption. And its duration is shorter – and action faster-than either regular or rapid-acting formulations.

The idea of a very fast acting insulin – faster than rapid-acting analogs currently available – is exciting to us for a couple of key reasons. First, currently marketed products still involve a lag between when most patients eat and when the insulin starts working. Minimizing this lag better mimics a non-diabetic's physiology. How excellent! Why? As we heard repeatedly throughout many different sessions , drugs with more physiologic profiles help mitigate hypoglycemic events. Plus, we just think less variability has to be better, even though no one will prove it because, as they look at you and sigh "…That's a long trial. And no one's going to do another DCCT." So second, as we think down the road, we need very fast-acting insulin to make an open-loop artificial pancreas viable. Viaject could be a needed step in that direction .

How does it work faster? Biodel was sufficiently reticent about formulation, but the company did share some high level details in its presentation. The rate at which injected insulin works depends on how quickly the hexameric links between the insulin and zinc stabilizers break down. Viaject's formulation pulls the zinc away from the insulin completely, favors this monomeric form, masks change, and resists the reformation of the hexamer – all of which speed absorption. In contrast, an insulin such as Humalog merely weakens the links between zinc and insulin – the hexamer form is still around, just weak. The cleaner, faster breakdown of Viaject seems to be the key to its fast uptake.

The oral presentation we heard on Biodel was phase 1 data on 10 people. Biodel's study design consisted of five euglycemic glucose-clamps performed on 10 fasting healthy individuals, using a fixed treatment order of 12 IU Humulin, 12 IU Humalog, and 12, 6, and 3 IU Viaject. All insulin was injected directly into the abdomen. Results showed that subcutaneous injection of Viaject caused a much quicker rise in glucose consumption than Humalog. When doses were equalized, Humulin reached its peak at 120 minutes and Viaject at 30 minutes. We wonder, of course, what the Humalog or Novalog peak would've been. As we mentioned above, Viaject also dissipated more rapidly. The data are limited and the sample size is small, to be sure. But that the faster onset and tighter duration could reduce the risk of post prandial excursions and hypoglycemic events is oh-so-appealing…

Viaject also showed higher metabolic activity within two hours after injection than that of Humulin and there was a clear dose-relationship between the dose of Viaject (12, 6, or 3 IU) and observed serum insulin levels and metabolic activity. Although the data were limited, patients seemed to tolerate Viaject well and no adverse events were reported. Yes, small trial, but a start! Also, Viaject is currently being

shipped in powder form, which has a two-year shelf life in room temperature. Once the powder is mixed to become liquid form, the compound is just as stable as regular insulin.

Conclusion? It looks like the pharmacodynamic effect of Viaject is significantly higher than that of Humulin and Humalog. Phase 2 data were shown briefly, offering the same conclusions as Phase 1. We are encouraged by how quickly the company seems to be working to get more patient data.

We will continue to watch Viaject closely because the formulation looks promising and appeals directly to some of the pressing issues highlighted at this year's meeting.

Now on to Levemir and Lantus – a hotly contested rivalry at ADA. Novo Nordisk's two-story, all-white, and incredibly crowded exhibit structure towered over the plain, not-so-crowded Sanofi Aventis exhibit. Symbolic of the battle between Levemir and Lantus? We think so. In a private lunch with clients of Rodman & Renshaw and Close Concerns, Dr. Drexler reminded us that Levemir may be appealing because it has a different effect on weight—in studies, it appeared to be weight neutral, and some patients even lost a little bit . Dr. Drexler believed that Sanofi-Aventis was misleading in promoting Lantus as a 24-hour drug, since he said it has a 16-hour duration! We hear from patients it does tend do vary. He said that Levemir is shorter-acting. Levemir is better on fasting glucose, but he said that Novo is doing a poor job of marketing the drug. He said that Levemir is a better drug. Hmm! We do see growth of long-acting analogs at risk due to Byetta – not that they won't grow, but just that they will grow more slowly.

Of note, though not talked about much, was the presentation by BD on intra-dermal insulin application. BD has recently completed a study on a new microneedle delivery system. This new needle is so small (1.5 mm) that it injects insulin into the skin, as opposed to subcutaneous (SC) regions. These results also look promising: in contrast to subcutaneous injection, intra-dermally applied insulin displayed more bioavailability in 10 healthy male patients. Also, insulin levels after intra-dermal injection of rapid-acting insulin peak significantly earlier than subcutaneous injection. Researchers are thus far unaware of the mechanism causing this rapid action, but Dr. Ronald Pettis guesses that these microneedles may inject directly into the lymph system – an interesting new approach. The major downside to microneedles is that patients would not be able to use the needle themselve**s, at least at this point – stay tuned on this one.**

While its microneedles are still in the research phase, BD is the only company currently with a needle as small as 5 mm on the market. This tiny needle only works for thin individuals as it will not inject deeply enough into heavier patients. The benefit of such a needle is that patients aren't scared of it – its so small they barely realize they are being injected.

TZDs – Thumbs Up? Thumbs Down? Thumbs Up?

So on this one, we sort of want to take a bye til Copenhagen in September. The drugs obviously work in some patients – not in others. We laugh at the earnestness at which some clinicians try to cajole patients into accepting weight gain of "the good fat." Loud laughter, etc. That said, Byetta combined with TZDs looked not so bad. And the drugs do work on insulin resistance, and there is one, Metaglidizen, where the side effect profile is meant to be much better than all the others. But let's just wait – we'll see the DREAM trial results in Copenhagen at EASD in mid-September and then we can decide how much bigger this class will get. Right now, $4 billion, and growing – if we introduce pre-diabetes? All bets are off. Even though based on DPP and Rezulin, we do think this trial, which will measure progression to diabetes, will show that TZDs are protective, we aren't SO sure because all the other outcomes trials recently have had unexpectedly negative results – DIGAMI2, PROACTIVE, FIELD. In all the cases, the design was ultimately deemed "off" - we'll be studying this one more carefully in the coming few weeks – the stakes are so high, after all!

Continuous Monitoring – Waiting for STAR (or, reimbursement)

Second only to the incretin mania, continuous glucose monitoring (CGM) was a focal point of ADA. We expected nothing less and were in fact a bit surprised that CGM didn't make an even bigger splash. DexCom and Abbott both showed new data in the scientific sessions, and Medtronic presented additional synthesis of the Guard Control data presented at EASD in its 5:30 am breakfast symposium.

In our view, this ADA was really DexCom's coming out party. Even so, there was no DexCom sponsored symposium, and the DexCom booth saw relatively little activity, perhaps a result of its poor positioning in the exhibit hall. On the other hand, DexCom won two oral abstracts in the scientific sessions, and the data surpassed what DexCom had demonstrated before in accuracy and clinical utility.

Dr. Howard Zisser presented a pilot study of 21 patients with type 1 diabetes that showed a mean ARD of 19.5% and a median ARD of 14.8% when sensor points were compared to SMBG (69-OR). The Pearson correlation coefficient was 0.89. The study was split into three 12-hour periods in which patients used SMBG only, CGM only, and CGM adjunctively. Investigators analyzed 104 patient self management decisions (SMDs) made during the placement phase. Of those, 33 (32%) were reduced by staff prior to delivery and 71 (68%) were unmodified. A decision was considered appropriate if three hours post-decision the sensor glucose was between 80 and 200. In periods 1 and 21, the percentage of appropriate SMDs was 53% for SMBG only and 71% for CGM only ($p=0.0052$). There was also a 2.3 hour (40%) increase in the time spent between 80 and 200 mg/dL and a 2.5 hour decrease in time spent below 80 mg/dL.

Dr. Satish Garg presented the data on the seven-day continuous sensor (71-OR); in this study, sensor-SMBG point analysis found a mean ARD of 15.7%, a median ARD of 11.4%, and 97% of points in the A+B zone (75% A zone alone). Dr. Garg showed that CGM significantly reduced the time spent in dangerous glucose ranges. In patients with an A1C >9, the amount of time spent in the 81-140 range increased by 94.6% ($p<0.05$), time spent 55-80 increased 27% (nonsignificant), and time spent < 55 decreased by 31% (NS). Surprisingly, there was no change in the time spent between 141 and 240 mg/dL, but the time spent above 240 dropped by 36% (NS).

At the Abbott symposium on Friday night, new data on Abbott's FreeStyle Navigator impressed us and everyone else jammed into the room. Here again, fists were nearly flying to make it into the room. In a major multi-center inpatient accuracy study, FreeStyle Navigator (FSN) was compared to venous blood using a lab reference YSI (n=58, 5 days), and a second multi-center study evaluated its performance versus SMBG in a home-use setting (n=138, 41 days). Eighty-two percent of the data in the accuracy study landed in the Clarke Error Grid zone A, with 98% in zones A + B. And the most excellent part? Eighty-two percent % of hypoglycemic (<70 mg/dL) episodes were detected as well (n=170). The median ART was 12.8% - nice one!

In the home-use study (2-LB), there were definite improvements in blood glucose control, with a 47% reduction in time spent <55 mg/dL, 19% less time spent between 55 and 80 mg/dL, 6% more time spent at 81-140; 8% more time spent in 141-240 (this wasn't intuitive to us) and a 19% reduction in time spent over 240 mg/dL. While the Navigator is not yet out, there was considerable excitement at the Abbott booth, where demonstrators were walking through an animation that showed the features of the device. One clinician we overheard was pleasantly surprised at the built-in FreeStyle meter, and everyone wanted to hold the small, sleek Navigator receiver in their hand.

On the Medtronic front, not much new data was presented, but its 5:30 breakfast symposium, featuring Drs. Richard Rubin, John Pickup, Jan Bolinder, Bruce Buckingham, and Jan Bolinder, was extremely well attended. There, the speakers framed CGM as a step down the road to the artificial pancreas, and at the Medtronic booth in the exhibit hall, we checked out its integrated pump-sensor technology. Most notably for us, we see Medtronic's enormous customer service/support/education/IT resources as a key selling point for both doctors and patients. The option to have an integrated pump and sensor appeals as well, and though we suspect, at least over time, DexCom and Abbott will be moving to join with various pump companies, Medtronic's single-company option will play well. Doctors also seem to adore the CareLink software that combines insulin dosing information with continuous glucose trending. That said, we were chagrined to realize that Medtronic's sensor still has the least appealing form factor—with the tube connecting the inserted sensor to the bulky transmitter—though we were reassured by Medtronic staff that the next generation will be smaller. Oh, good!

Medtronic's investor update clarified for us that the real-time CGM values are not, in this generation of software, put into the bolus wizard. (The CGM data beams to the screen, but users must input their capillary values to calculate an insulin dosage.) This is what we would expect given the adjunctive labeling, but we hope to see accuracy that can support direct inputs from a CGM into a pump bolus wizard in the near term. The latest published accuracy figures, included on Medtronic's fact sheets distributed at its ADA booth, show mean and median ARD of 19.7% and 15.6%, respectively.

We also loved the glossy blue book given out at Medtronic's booth that featured all of the insulin pump therapy and continuous glucose monitoring abstracts published at ADA 2006, which just highlighted for us that every study on CGM, done with any device, advances the entire field.

LifeScan Adds Luster to its Blood Glucose Monitoring

We love LifeScan's Ultra 2 and definitely think patients will be more engaged using it, It is adding new features that will help anyone, especially intensively managed patients, with their control. The Ultra 2 uses the same strips as the currently popular OneTouch Ultra and generally makes it easier to use. From the finger stick results screen, a single button push lets users indicate whether the test is pre-or postprandial - nice one! The Ultra 2 also has more advanced portion-indicating features—which are thankfully easy to use. Plus, they've done a great job marketing, with Patty LaBelle – check out the website if you haven't seen the commercials on CNN or CNBC. What's the newest risk for blood glucose monitoring? In a word, Byetta. It's good new/bad news – the good news is that it is also looking like Byetta might emerge as a risk to BGM testing. If the wonder drug gets widely prescribed people may become far less careful about always doing mealtime finger sticks.

LifeScan notwithstanding, blood glucose monitoring (BGM) did not receive much attention this year ; it was definitely continuous meters—BGM's sophisticated new cousins—that stole the show. Still, there were some interesting BGM developments in the scientific sessions, and we'd say that the meter market still has plenty of life left, especially since reimbursement for continuous meters (CBGMs) has yet to emerge. See our CBGM section for more information on what we and others see as at least a somewhat finger stick-free future.

The main inroad BGM had at ADA was in the multiple scientific sessions on Self-Monitored Blood Glucose (SMBG) testing in type 2s who are not on insulin. A heated debate developed about the relative merits of encouraging patients to test at home; it seems obvious but the data actually aren't really convincing. One debate between Dr. Richard Bergenstal (International Diabetes Center—Minneapolis) and Dr. Antonio Nicolucci (Italy) was particularly interesting. Dr. Bergenstal started the session by presenting data from the ACCORD and RoSSo studies showing the efficacy of SMBG. Dr. Nicolucci followed and methodically showed the weaknesses in all the SMBG-advocating studies: small sample

sizes, major washout periods, high dropout rates and short observation periods. His most contentious argument was about quality of life issues: the type 2s who used SMBG actually had higher rates of diabetes-related stress, health worries, and depressive symptoms. We believe this is probably spurious correlation. One of the key posters supported Dr. Nicolucci's arguments: #1946 from Duesseldorf, Germany, showed that a high frequency of self-managed finger sticks did not leave patients with lower A1c's than their infrequently-testing counterparts. The half of the study completed so far has led the doctors to the conclusion that one stick a week was just as effective as four in maintaining the metabolic control and A1c level. Aside from being surprising, the poster made another point: the economic effects of this could be huge, saving countries (especially those with national health care like Germany) hundreds of millions annually. While it could save short-term, we suspect that over the long-term, the savings will be completely diminished by far higher expenses relating to long term complications. Unfortunately, there certainly wasn't any consensus reached on the issue at the meeting, and the introduction of CBGMs will complicate the picture even further.

Pumps Continue to Look Promising

An information-packed session titled "Pumps in pediatrics" reviewed many of the current benefits of pumps in children and adolescents. Other than the risk of hypoglycemia, not many objections were raised. Still, only about 20% of type 1 patients are on pumps, and very few type 2's – we continue to believe that a new paradigm, disposable pumps, could expand the market considerably. Toward this end, there was much interest in Insulet on the exhibition floor.

Dr. William Tamborlane of Yale touted the across-the-board benefits observed in patients using pumps, even suggesting that pumps could simulate the plasma insulin in non-diabetic youth. He said that for a long time people were hesitant to use it because of uncertainty about the benefits of intensive therapy, mostly on the part of physicians. Now, that uncertainty is gone, he said, and researchers know that pump therapy produces a much more stable glucose level.

Not only does the treatment work, Dr. Tamborlane stressed, but patients also like it. One study showed that two thirds of children chose pumps over multiple daily injections (MDI). The Berlin Consensus Recommendation, which is not yet published, recommends pump therapy for "just about everyone." It is strongly recommended for those with recurrent severe hypoglycemia, with A1C above target, with unacceptable fluctuations in blood glucose, with microvascular complications, and with a compromised lifestyle due to diabetes.

Dr. Peter Chase of the University of Colorado reviewed the major benefits offered by pumps in delivering meal boluses. A study in *Pediatrics* in 2004 showed that A1C was directly proportional to the number of missed boluses. In one study, A1C levels rose an average of 0.5% in patients who missed two boluses per week and an average of 1.0% in patients who missed four boluses per week. Dr. Chase is certain that pumps will reduce the number of missed meal boluses.

Evidence supports his claim. Younger patients on a pump were hyperglycemic in 7.8 out of 100 tests while those taking MDI were hyperglycemic 8.9 out of 100 times. Dr. Chase guesses that A1C improvement with pumps will be greater in younger children than teens. Only 20 to 30% of patients on a pump do not improve or get worse. Strangely, his study found that the success of the pump had no relation to whether boluses were taken before or after meals (the p value was .052). This is a benefit for very young children, where it is difficult to know when they will eat. However, Dr. Chase emphasized that it was very important for older children to take boluses before meals. Alarms on pumps could be an extra measure to prevent missed boluses.

Sadly, deliberate bolus skipping also occurs, more often in young women, as a (very unhealthy) way to lose weight. In one study, seven out of 66 girls and one out of 69 boys skipped for this reason. Both Dr. Tamborlane and Dr. Chase brought up the development of an external closed-loop system. Both doctors anecdotally shared that they believe a short-term closed loop is feasible.

PART THREE: Posters of Note

We've taken out a lot of the poster discussions due to space this month, but we decided to leave in a few related to Byetta to give those who didn't attend the meeting a whiff of incretin fever …

487-P. SAFETY AND EFFECTS OF A ONCE-WEEKLY LONG-ACTING RELEASE FORMULATION OF EXENATIDE OVER 15 WEEKS IN PATIENTS WITH TYPE 2 DIABETES. Dennis Kim, Leigh Macconell, Dongliang Zhuang, Catherine Schnabel, Kristin Taylor, Wen-I. Li, Michael Trautmann.

A zoo. Standing room only, complete fire hazard. This poster was by far the most popular. Neighboring poster presenters looked lonely in comparison. That said, about half of the people jockeying for position at 487 were analysts.

AE. Lots of questions about the strange and high percentage of adverse events reported. Before getting in to the data, Dr. Dennis Kim pointed out – and had to do so many times – that because of the low n, one patient equals a 6-7% change in adverse event percentages. So, the incidence of 25% hypoglycemia for the low dose LAR is four patients. Further Dr. Kim described Amylin's attitude about hypoglycemia, which is, if a patient so much says, "I felt a tiny bit woozy," it counts as hypoglycemia. None of the four required medical attention and only one was documented with a glucose monitor.

Needle size, drug volumes. Many questions about needle size and drug volume. The answer was always the same – not releasing information on drug stability, needle size (but pain wasn't mentioned enough to make the AE list) and not releasing information on microsphere size. Dr. Kim noted that despite the 100x (This might be overstated due to poor hearing at that moment – but not by much!) increase in drug volume required to make the LAR, the LAR volume was still small.

The injection is subcutaneous. For purposes of this trial, a healthcare worker gave the shot. However, the marketed platform will be for home administration.

Still on needles. We asked a representative from Alkermes (medical director?) if the company had made any drugs in pen form yet. Answer? Microspheres require reconstitution so pen's aren't applicable. He said "…but we're working on it."

What's next? Starting with 1 week formulation but because the exposure to LAR lasts beyond 1 week, a once monthly formulation is possible.

Post-prandial glucose. At the low dose, the PPG variability was less than placebo in terms of levels but the curves were similar. At the high dose, the curve was much better, but not flat relative to baseline like BID. Dr. Kim said that despite the variability, the high dose pattern mimicked numbers seen in non-diabetics. (Roughly, 80-120, with 80 around a meal). We asked why he thought the pattern was different than that seen in Byetta. He thinks that BID is more dynamic and physiologic compared to sustained.

Weight loss. At the low dose, weight loss didn't differ much from placebo. The high dose showed average weight loss of 3.8 kg +/- 1.4 kg, with a continued downward trend. Dennis attributes the difference to ultimate plasma concentration levels. All but one high-dose patient lost weight, two lost ten

or more kg. (These were the outliers in the high-dose category; there were no outliers in the low-dose category.)

Low versus high dose. Of the four or five mechanisms of action for GLP-1 inhibitors, glucagon's suppression was pretty much the only one that the low dose was able to effect – because according to Dr. Kim, a very little bit goes a very long way. The higher dose achieved glucagon's suppression, insulin secretion, gastric emptying, and appetite suppression.

More data? We should see data in the middle of next year. The study will be non-inferiority to Byetta BID. Dennis wouldn't share expectations for numbers in trial, but said it would be powered similar to any other non-inferiority trial. (In other words, a stats wizard could calculate the number pretty easily.) In terms of this trial, getting participants was easy – Byetta's reputation for weight loss lowered the bar for attracting patients.

488-P. EXENATIDE (EXE) USE IN T2DM WITH A1C ≤ 7%; Robert C. Hood (Beaumont, TX).
Dr. Hood is a very aggressive, very strict doctor. He considers A1c's over 6.5% unacceptable. He puts patients on orals and gives them three months to get their act together (very rigorous diabetes education including diet and exercise). If not at 6.5% or below, they go on insulin. His average patient is at 6.2%; 72% of his patients are under 6.5%; and 46% are in the normal range! Only about 4% have dropped Byetta due to GI side effects. Many who have GI side effects want to do anything it takes to stay on the drug because they want to retain the feeling of being sated all the time. Of his patients that didn't lose weight, he attributes this to (1) no satiety control or (2) continued overeating even though feeling full. He wouldn't bump DPP4's ahead of Byetta because of the weight-loss impact.

507-P. CLINICAL EXPERIENCE WITH EXENATIDE: THE FIRST 100 PATIENTS
Allen B. King, Susan Healy, Esther Perez, Dana Armstrong. (Salinas, CA)
Dr. King said he's got data on about 200 patients out to six months that will be published in a month or so. Overall, he's got 400 patients on Byetta with data out to one year on some of them. His experience is that patients have been able to maintain their weight loss, their A1c reduction, and their ability to reduce the dose of other anti-diabetes drugs they were taking (all classes). This 400 total patients include those with metabolic syndrome, pre-diabetics, type 2s, and even some type 1s. He thinks it's a great pre-diabetes drug and has great success in this capacity. Provocative and we're staying so tuned….

PART FOUR: Selected Sessions

PRESIDENT, MEDICINE & SCIENCE ADDRESS

Cure, Optimal Care and Total Commitment—What If They Happened Tomorrow?
Robert A. Rizza, M.D.

Dr. Robert Rizza, current ADA President, gave a dramatic, effective, well-received address on the need for the U.S. to fully commit to finding a cure for diabetes and improving diabetes care. He began his talk with statistics. More than 20 million people in the United States have diabetes, and more than 40 million have prediabetes. In 2002 alone, diabetes costs totaled $132 billion. Diabetes is the number one cause of new blindness in adults 20-74 years of age, the number one cause of kidney failure, and the number one cause of nontraumatic lower-limb amputations. It is projected that one in three children born today will develop diabetes; in high risk groups, one in two children will develop the disease—unless we do something to stop it.

In emphasizing the great threat diabetes poses to our population and the problem with governmental inaction on this front, Dr. Rizza compared diabetes to a "biologic weapon." Clearly our government

would take swift action if an enemy used biological warfare against our nation, so why not for diabetes? To illustrate his point, Rizza used an evidence-based healthcare model called Archimedes to quantify the predicted benefits of a cure for diabetes and optimal diabetes care. Archimedes is a robust mathematical model of physiology and healthcare delivery, created for Kaiser Permanente in the early 1990s by David Eddy, MD, PhD, and Leonard Schlessinger, PhD. Equations simulate metabolic pathways and processes leading to diabetes complications, and the model is linked to the NHANES database so that it can create "clones," or virtual people. As for its validity, Archimedes has independently predicted the results of randomized controlled trials that were not used in the model, including accurate prediction of DPP results before they were even published.

Archimedes estimates that over the next thirty years, diabetes will lead to 57 million deaths, 127 million serious adverse events, 35 million heart attacks, 15 million strokes, and 2 million amputations. The model predicts that it will cost $6.6 trillion over the next thirty years to treat the complications of people alive today with diabetes. On the other hand, it predicts that if diabetes were cured tomorrow, over the next thirty years there would be a 45% reduction in serious complications of diabetes, 41 million fewer life-changing adverse events, 17 million fewer heart attacks, 1.4 million fewer strokes, 7.5 million fewer cases of blindness or eye surgery, and essentially no more end-stage renal disease. If diabetes were cured tomorrow, the predicted cost savings over the next thirty years is $700 billion.

While it's nice to consider, diabetes is not going to be cured tomorrow, so Dr. Rizza took his predictions a step down, quantifying the predicted benefits of giving 100% of patients with diabetes optimal care. Optimal care was defined by ADA recommended goals: A1c <7%, blood pressure <130/80 mmHg, LDL <100 mg/dL and statin therapy for LDL-lowering, HDL of >40 mg/dL in men and >50 mg/dL in women, triglycerides <150 mg/dL, smoking cessation, and aspirin therapy. If all patients received optimal diabetes care, Archimedes predicts that over the next thirty years there would be 8 million fewer heart attacks, 1.6 million fewer strokes, 2.2 million fewer cases of renal failure, 2.4 million fewer cases of blindness or eye surgery, 100,000 fewer amputations, 3.5 million fewer deaths, and 18 million fewer serious diabetes complications. Overall, there would be a 57% reduction in the risk of diabetes complications and a $325 billion reduction in medical costs.While it is also nice to entertain the idea of every single patient meeting ADA treatment goals, that isn't going to happen either. What if 80% of patients met ADA goals? Rizza termed this idea "committed care." Without the smoking cessation requirement, if 80% of patients achieved ADA goals, Archimedes predicts 11 million fewer serious diabetes complications and a cost savings of $150 billion over the next thirty years. Of course giving care to 80% of patients costs a lot of money, so Rizza presented cost analysis. Lowering A1c to <7% in 80% of diabetes patients saves money. Lowering A1c to <7% while also lowering blood pressure to <130/80 in 80% of diabetes patients also saves money. Meeting A1c, blood pressure, LDL, HDL, and triglyceride goals, along with use of aspirin therapy in 80% of patients is cost neutral. Therefore, we would save lives and complications while not even spending more money.

Lastly, Dr. Rizza raised the idea of giving a polypill containing metformin, a low-dose aspirin, a generic statin, and a generic ACE-inhibitor to 80% of diabetes patients. This polypill would cost about $100 per patient per year and would lead to 1.2 million fewer deaths over the next thirty years, 7.2 million fewer diabetes complications, and cost savings would begin to accrue after 5 years and would increase each year thereafter.

Rizza pointed out that it costs less to treat diabetes than it costs to treat the complications of diabetes that result from not treating the disease in the first place. Thus, treating diabetes is a wise investment. Dr. Rizza predicted many diabetes scientific breakthroughs in the future in the areas of islet cell biology, intracellular signaling, systems biology, and neural signaling, and he stressed the need for the United States to invest more in diabetes research. He eloquently stated that the size of this investment should be commensurate with the risk diabetes poses to our society.

BANTING LECTURE: Harmony and Discord in the Orchestration of Glucose Metabolism, Richard Bergman, Ph.D.

Richard Bergman, Ph.D., was awarded the Banting Medal, the highest award given by the American Diabetes Association. The award is considered to be long overdue for a man whose work has helped to shape our understanding of the pathophysiology of insulin resistance. Dr. Bergman began his lecture by explaining that he was trained as an engineer, and his approach to understanding the changes that occur in diabetes came from an engineering standpoint. He explained in trying to "reverse-engineer" the biology of diabetes, he developed a simple mathematical model of how the pancreas copes with insulin resistance, then tested these equations against real-world data, which took the forms of physiological experiments in the dog. This simple model became known as the "minimal model" where the function of the beta cell was modeled on two parameters: insulin sensitivity (SI) and baseline glucose usage by the body without insulin (SG).

From this minimal model, it was observed that beta cell function could be described as a hyperbolic relationship between insulin sensitivity and insulin secretion. Simply put, the beta cell should secrete more insulin when the body is insulin resistant, and less when it is insulin sensitive. When multiplied together, the product of the insulin sensitivity and insulin secretion (both measured in a controlled experimental setting), you would get a constant number, termed the disposition index (DI). Every person will have a different disposition index that reflects their ability to compensate for insulin resistance. Generally, the higher the DI, the better your function of beta cells. However, the problem with diabetes is that the disposition index changes, where the beta cell is no longer able to compensate for insulin resistance.

Bergman and his colleagues have tested thousands of humans—diabetic and non-diabetic alike—and found that the disposition index can reliably predict the onset of diabetes. Moreover, a person's DI is a heritable trait. In the Insulin Resistance Atherosclerosis (IRAS) Family Study led by Dr. Bergman, 21 pedigrees of African-American families were analyzed for defects of the DI. The defect has been linked to Chromosome 11q, which has also been linked to type 1 diabetes. This same locus was independently identified as a possible region for the DI by a group from Finland, which strongly supports Dr. Bergman's findings (it is rare to have two groups with large patient populations independently come to the same conclusion). The LOD score (logarithms of the odds ratio) for this correlation between DI and Chromosome 11q is 2.7, which is very high, meanly that it is almost 1000 times more likely that the gene is on Chromosome 11 than it is somewhere else.

Another phenomenon that Dr. Bergman characterized is the process of transendothelial transport (TET). An important aspect of the physiologic models of insulin sensitivity was that it reflect the real-time kinetics of insulin action. Bergman and others observed a conundrum that initially could not be explained: if you expose cells or tissues to insulin in a culture dish, they respond very rapidly (within 5 minutes). However, following an injection into the bloodstream, insulin works over the course of 60-120 minutes to lower blood sugar. Why is this? Dr. Bergman proposed that one limiting factor is the movement of insulin from the circulation to the interstitial fluid (the fluid that bathes most tissues, including muscle and fat—continuous glucose monitoring samples glucose from the interstitial fluid).

Dr. Bergman and his associates measured insulin concentrations in blood and interstitial fluid and found that while insulin appeared in the blood very quickly, it appeared in the interstitial fluid slowly. They found that the appearance of insulin in the interstitial fluid is the rate limiting step to insulin action in the body (i.e. reducing blood sugar). Once you transport insulin across the endothelium to the interstitial fluid, then insulin works on the tissue like it were in a culture dish. Dr. Bergman speculates that this is why first-phase insulin secretion might have evolved—that you get a quick burst of insulin initially that

takes 30-60 minutes to get to the tissues, just in time to deal with newly digested/absorbed glucose from a meal.

Interestingly, TET is reduced in obesity. Measurements from Dr. Bergman's lab reveal that reduced TET accounts for almost half of the insulin resistance in fatty rats. Thus, Dr. Bergman concludes that changes in signaling activity can only partially account for insulin resistance—that you must always consider the physiologic and architectural problems that occur in diabetes when you consider insulin resistance.

Dr. Bergman was also interested in the physiological mechanisms of the dreaded metabolic syndrome, also called Syndrome X (Dr. Bergman playfully called the condition the Metabolic Xyndrome as a compromise). To begin his study, Dr. Bergman focused on the physiology of the liver in obesity. This stemmed from the TET problem mentioned earlier. The liver does not undergo tranendothelial transport, and should thus be activated by insulin quickly. However, in insulin resistance, this does not occur. Dr. Bergman was convinced that there must be another signal mediating the insulin resistance. After going through many potential candidates, Dr. Bergman found that free fatty acids may be the culprit.

Free fatty acids are now recognized as a crude hormone, as they directly stimulate glucose production in the liver, insulin secretion in the beta cell (via the GP40 receptor), and also promote insulin resistance (via the toll-like receptors and TNF-alpha receptors).

High-fat feeding or free fatty acid infusion into dogs led to changes primarily in the liver, where genes for lipid synthesis (such as SREBP and fatty acid synthase) and gluconeogenesis (PEPCK and G6Pase) were upregualted. These data are consistent with many population based studies that pinpoint insulin resistance of the liver as a primary defect in insulin resistance.

Dr. Bergman then discussed why visceral adiposity could lead to insulin resistance. It is widely known and accepted that the omental (belly or "apple-shaped") fat lead to increased insulin resistance and adverse cardiovascular outcomes. This fat depot, when insulin resistant or stimulated by the nervous system, spills free fatty acids (the product of lipolysis) directly in to the portal vein, which heads straight to the liver, making it insulin resistant. Interestingly, lipolysis of visceral fat occurs in waves—every 10 minutes—and is highest at night. Free fatty acids, then, may be the driving force behind insulin resistance response since they make the liver insulin resistant (leading to increased fasting glucose) and directly stimulate the beta cells to produce more insulin (compensory hyperinsulinemia).

Dr. Bergman then concluded his lecture by applauding the ADA for funding risky research projects that will continue to advance science. He readily admits that, looking back, his "minimal model" hypothesis was way too simple to have worked as well as it did and most other funding sources might have rejected it outright. He thus encouraged other young investigators to think big and not be afraid to think outrageous as well.

As one of the premier physiologists of the last thirty years, Dr. Bergman has helped to advance our understanding of both the physiology and pathophysiology of the beta cell in diabetes. Perhaps his work can be used to better model beta cell function in vivo, which would be an especially useful endpoint in clinical trials to treat diabetes. Indeed for the work he has done and the work he continues to do, the Banting Medal is certainly well-deserved.

PART FIVE: EARLY STAGE SCIENCE

Interorgan communication to regulate glucose homeostasis - Overview
Diabetes may ultimately come from defects in the beta cell—either from the beta cell not secreting insulin (type 1 diabetes) or not secreting a sufficient amount to compensate for the body's insulin resistance (type

2 diabetes). However, the beta cell is not the only organ involved in regulating glucose homeostasis. The body has adapted sophisticated ways to regulate glucose levels in the blood. The brain requires glucose for its metabolic needs and many organs in the body work together to make sure the glucose levels stay constant. In fact, much of the basic science sessions at ADA had a theme of metabolic homeostasis as the result of harmony between various organs.

The liver, previously an underappreciated player in diabetes, is now recognized as a critical regulator of the severity of diabetes. When you fast, the liver is responsible for maintaining blood glucose levels by both breaking down stores of glycogen (glycogenolysis) or by making new glucose molecules from amino acid and fat precursors (gluconeogenesis). The signal to tell the liver to stop making glucose is insulin. Thus, if insulin does not act on the liver (either from inadequate insulin, liver insulin resistance or a combination of both), then the liver will continue pumping out glucose even if there is a lot of glucose in the blood. In diabetics, this contributes greatly to postprandial hyperglycemia and is a major factor in glucose intolerance. Not surprisingly, this area of science was recognized by awarding the science achievement medal to Markus Stoffel, M.D., Ph.D. of Rockefeller University, who has identified several important genes that regulate hepatic insulin resistance.

In addition, it is now appreciated that the brain, particularly a region called the hypothalamus, plays a huge role in regulating glucose levels. First, the hypothalamic contains the areas of the brain that regulate satiety and appetite. By altering the hormonal signaling within the hypothalamus, the brain can significantly alter the course of diabetes. Even more intriguing, Lucianos Rossetti, MD, of Albert Einstein University, has published several high-profile papers over the last three years indicating that the brain also controls when the *liver* secretes glucose. As will be discussed later, the just-as insulin tells the liver to stop producing glucose. As a measure of insurance, it also tells the brain to tell the liver to stop producing glucose. A debate between Luciano Rossetti and another famous scientist, Alan Cherrington, Ph.D., was a highlight of the conference and is discussed below.

The importance of interorgan endocrine communication is also highlighted by the fact that the Banting Medal was a awarded to Richard Bergman, Ph.D., of the University of Southern California, who is a pioneer in the study of how the different tissues in the body, particularly the liver and pancreas, can communicate with each other via hormones to regulate glucose homeostasis. This will be highlighted in a following section.

The dual regulation of glucose homeostasis by the brain and the liver

Claude Bernard, the famous French physiologist, discovered almost 140 yrs ago that the disruption of rabbit hypothalamus could lead to diabetes. It is only within the last five years that we are beginning to understand why this was so. A highlight of the basic science sessions of the ADA conference was a debate between Luciano Rossetti, of Albert Einstein, and Alan Cherrington, of Vanderbilt University, who debated whether insulin regulated liver function solely through the direct actions on the liver, or by indirect actions through the hypothalamus.

Alan Cherrington, Ph.D.

Dr. Cherrington argued that there is no CNS-mediated effect of insulin on hepatic glucose production, only a direct insulin-to-liver effect. He began his talk by explaining the known physiological effects of insulin on the liver. It is known that insulin is the major signal to suppress the hepatic glucose production (HGP) of fasting. As mentioned earlier, the failure of insulin to suppress HGP is a major defect in type 2 diabetes.

Insulin can directly act on the liver through its receptors to inhibit glucose production. The liver creates glucose from two sources: the breakdown of glycogen stores (glycogenolysis) and the creation of new glucose from fat and amino acids (gluconeogenesis). Insulin is known to decrease the expression of key

genes of gluconeogenesis, including phosphoenolpyruvatecarboxykinase (PEPCK) and glucose 6-phosphatase (G6Pase), as well as stimulate the production of glycogen. These processes are thought to occur through known signaling pathways, since mice that lack the insulin receptor in liver (LIRKO mice), or mice that lack PI3K, a major component of insulin signaling (Taniguchi, et al, *Cell Metabolism* 2006) have profound fasting hyperglycemia and diabetes due to uncontrolled HGP.

Dr. Cherrington uses the clamp technique in the conscious dog. The dog is an attractive model because the animal is large enough for complicated surgery and can be used to obtain sufficient blood samples to accurately measure glucose and other metabolites as they are produced. It is called the clamp technique because the experimenter can keep almost all metabolic values constant (such as glucose, insulin or free fatty acids), and they can also regulate them in specific parts of the body. For instance, you can make the portal vein or the brain very high in insulin, while keeping all other areas constant. This can be done in almost any combination with any metabolite or hormone that you can think of. Of course, the technique is very complicated and only a few labs in the world can do it right.

There is a litany of literature showing that insulin has a marked direct effect on the liver. If you deplete just portal insulin (insulin going to the liver), but keep all other insulin constant, you increase HGP, and if you increase portal insulin the reverse is true. The mechanisms by which insulin shuts down HGP is about 80% due to the inhibition of glycogenolysis and 20% due to the inhibition of gluconeogenesis.

On the other hand, there are other significant mechanisms by which insulin regulates HGP. The first is glucagon secretion, where insulin inhibits the release of glucagon, a potent stimulator of HGP (also an important target of GLP-1 agonists). In addition, insulin inhibits the peripheral tissues from sending gluconeogenic precursors to the liver for gluconeogenesis. Lastly, insulin may talk to the central nervous system (CNS) to inhibit lipoplysis and hepatic glucose production. The contribution of the CNS was not known until Rossetti's recent papers.

To test the effect of insulin in the CNS on hepatic glucose production, Cherrington's group "clamped" the levels of insulin going to the brain at four time higher than the rest of the body. Everything was held constant (glucose, free fatty acids), and hepatic glucose production was measured—and there was no effect! When the nerves connecting the brain to the liver were severed experimentally, again, they found no effect.

For further proof, Cherrington cited a study in *The Journal of Clinical Investigation* (Peresghin,1997) in which hepatic glucose output was measured in liver transplant patients; investigators found that HGP was suppressed normally by insulin. This is significant because the transplanted livers in these patients do not have connections to the CNS and should not have any direct input from the CNS. The study was even well controlled for immunosuppressive therapy and other factors.

Luciano Rossetti

On the opposite side, Luciano Rossetti of Albert Einstein College of Medicine argued that the brain exerts significant influence over the functions of the liver. The Rossetti lab has studies how insulin action in the brain affects glucose homeostasis. Several recent papers in prestigious journals like the *Journal of Clinical Investigation (JCI)*, *Nature*, and *Science* have demonstrated that insulin infusion into the third ventricle of the brain (an area of the brain that makes the cerebrospinal fluid which bathes all neurons in nutrients).

Dr. Rossetti uses mice as his model organism. The advantage with mice is that you can create an array of genetic defects to complement the physiologic studies you perform. The downside is that mice are so small that it is technically very difficult to perform the clamp studies in mice than it is in dogs.

Several papers from Dr. Rossetti's lab caught the eye of the scientific world. Two papers published back-to-back in *JCI* revealed that knocking the insulin receptors in the liver with antisense technology (not a conventional knockout technique) had no effect on hepatic glucose production. Only when insulin receptors were knocked out in the brain was there any change in hepatic glucose production. This data was intriguing, though controversial, since it contradicted some data that used more conventional techniques. For instance, the liver-specific insulin receptor knockout mouse (LIRKO) mouse showed significant increases in hepatic glucose production.

Dr. Rossetti then presented several papers showing how alterations of the insulin signaling pathway in the hypothalamus exerted great influence over the liver. Decreasing insulin signaling by inhibitors or knockout (genes such as Akt2 or PI3K were inhibited) caused increases in hepatic glucose production (mimics insulin resistance) while activating the insulin signaling pathway shut down hepatic glucose production by greater than 50%.

Dr. Rossetti conceded that his paper's results might have been misinterpreted, as they never claimed that the brain was the only thing controlling the liver, but he argued that it is a major regulator. Moreover, he points out that the physiologic data are consistent: that neural inputs (indirect insulin effects) regulate gluconeogenesis, while direct inputs (insulin acting on the liver itself) regulate glycogenolysis.

Rebuttals
Dr. Rossetti explained that Dr. Cherrington could not replicate his experiments in mice in the dog model because the dose of insulin might have been too high. At supraphysiologic doses, insulin actually has the reverse effect when infused into the third ventricle.

Dr Cherrington then countered by wondering how physiologic an insulin infusion directly into the third ventricle is? Are the experiments merely demonstrating the hard wiring, or are the processes exposed by Dr. Rossetti relevant to diabetes? It is not known yet.

Dr. Cherrington also expressed concerns over the differences between dogs and mice, since mice tend to have a very high neural tone and a more rapid metabolism than dogs or even humans. This is because mice feed constantly (grazers) while dogs tend to eat one big meal a day. These fundamental differences may explain the more pronounced effects in mice. Also, he pointed out that Dr. Rossetti needs to understand what the neural mediators of the neural regulation are: is it muscarinic acetylcholine receptors or nicotinic acetylcholine receptors?

Molecular Mechanisms of Hepatic Insulin Sensitivity
Several different molecules were highlighted as major players in regulating hepatic insulin sensitivity. A few are discussed below.

Foxa2
This molecule was characterized by Dr. Markus Stoffel. Foxa2 is activated during fasting and turns on the fatty acid oxidation program in the liver. Foxa2 also restores insulin sensitivity to the liver. Unfortunately, Foxa2 is rapidly inactivated in the presence of even minute amounts of insulin due to its ability to be inactivated by either IRS-1 or IRS-2. Dr. Stoffel proposed that promoting the fasted state (by eating less often) will help Foxa2 stay active longer and promote fat usage by the body.

FoxO1
This molecule is a potent activator of gluconeogenesis. One of insulin major effects to activate a kinase cascade that phosphorylates and inactivates this molecule. Dr. Michiro Matsumoto of the Accili lab at Columbia University presented two oral presentation on this molecule (it is very rare for a scientist to be awarded two oral presentation, especially in the same session). Dr. Matusmoto first knocked down FoxO1

with and RNAi adenovirus in the hepatocytes and found that the loss of FoxO1 greatly decreased hepatic glucose production by increases PEPCK and G6Pase. He then overexpressed FoxO1 in the livers of otherwise normal mice and found that gluconeogenesis was strongly activated. The high levels of FoxO1 also resulted in the activation of lipid accumulation and lowered HDL levels. This effect on the lipids is probably due to the high levels of expression that Dr. Matsumoto achieved with his adenovirus system.

Akt and atypical PKC

In one of the opening symposia on hepatic insulin resistance, Dr. C. Ronald Kahn (my research mentor), presented my data on the fine control of hepatic gluconeogenesis and lipogenesis by Akt and atypical PKC, respectively. Insulin drives the liver's metabolic functions by activating a molecule called phosphoinositide 3-kinase (PI3K), which then recruits other enzymes to carry out its orders. While researchers knew that the PI3K pathway was important to insulin's action, until now they didn't know how insulin uses PI3K to control either glucose or lipid metabolism.

Using mice bred to lack specific subunits of the PI3K pathway, the researchers discovered that mice that could not activate Akt had increased glucose production in the liver, impaired glucose tolerance, and increased levels of insulin in the blood, all contributors to type 2 diabetes. On the other hand, those mice with defects in the enzyme PKC1/z, an atypical form of the protein kinase C (PKC), had decreased lipids in the blood and a decreased levels of a protein called SREBP, which is critical for regulating fatty acid and cholesterol in the blood. (This particular form of the PKC enzyme is distinct from the form known as PKC-beta, which is activated by high blood glucose and is linked to many diabetic complications, including those of the eye and the blood vessels.)

This clarified an area of controversy, since people used to think that Akt controlled both glucose and the lipids in the liver, but now we know that Akt has nothing to do with the lipids. Akt controls the glucose part and the atypical PKC controls the lipids part. This is relevant to disease and diabetes since some patients with fatty liver disease don't have any glucose problems, while others with type 2 diabetes don't have problems with their lipids. The specific regulator of glucose or lipid homeostasis in the liver will allow drug companies to look for ways to specifically target just the lipids or just the glucose problems.

Inflammation, Obesity and Insulin Resistance
Overview

One of the hottest areas of diabetes biology is the study of how the inappropriate activation of the immune system can lead to insulin resistance. It has been known that people with bad bacterial infections (sepsis) often become diabetic due to severe insulin resistance. When the infection is cleared, insulin sensitivity returns. When the immune system is triggered, cytokines (a type of hormone that activates the immune system) are released to further recruit other immune cells. Unfortunately, cytokines activate cellular pathways that antagonize insulin receptor signaling, which leads to insulin resistance. Further studies have revealed that obese patients have elevated cytokine levels. But why is this so, if these patients do not have an infection?

One theory to explain the increased levels of cytokines is that obesity somehow mimics an infection. The immune system recognizes bacteria by special lipid molecules on their cell wall (lipopolysaccharides) via a special set of receptors called toll-like receptors (TLR). The activation of TLRs causes the release of cytokines from specialized cells called macrophages. It is thought that the high circulating levels of lipids (free fatty acids) in obese people can inadvertently activate the TLRs to cause a release of cytokines, leading the activation of the immune system and insulin resistance. TLRs are not only expressed in immune cells, however, as they are also expressed in insulin sensitive tissues like muscle, liver and fat. TLR activation by infection or lipids activate the negative regulators known as suppressor of cytokine

signaling-3 (SOCS3), and c-Jun N-terminal kinase (JNK, pronounced "junk") which both interferes with both leptin and insulin function in most tissues.

In addition, obesity is linked to insulin resistance through a process known as endoplasmic reticulum (ER) stress. The endoplasmic reticulum is a specialized part of every cell that synthesizes lipid molecules (fat, steroid hormones), and also helps to fold proteins up into their correct structure. Recently, it has been recognized that obesity greatly increases the activity of the ER because of increased lipid synthesis (to put away all that extra energy) and increased synthesis of proteins (more food, bigger body). Obesity can overwhelm the ER, causing it to "stress out" and shut down—hence, ER stress. While it is not known exactly how what causes ER stress in the body, it is known that the induction of ER stress (by genetic knockout or by chemicals that cause ER stress) cause molecular changes that are very similar to cytokines, with an increase in the activity of JNK, which interferes with insulin action.

Session
The oral presentations at the morning session "Inflammation, Obesity and Insulin Resistance" provided data that supported the idea that inflammation leads to insulin resistance and diabetes. The session was packed for 8 a.m., probably because people were eager to hear the first speaker, Dr. Gokhan Hotamisligil, of the Harvard School of Public Health. Dr. Hotamisligil has published seminal work on the role of inflammation and ER stress in insulin resistance. His talk was an excellent and basic review of the inflammation and ER stress pathways, as I have described above. He presented some new data at the end of his talk (one slide) that showed that small molecule compounds that reverse ER stress can also reverse diabetes in obese diabetic mice (ob/ob mice). The data were also presented as a late-breaking abstract (34-LB), but the poster did not show anything that was not presented in Dr. Hotamisligil's talk. Interestingly, they do not know what the actual molecular target of the drug is; they just know that it prevents ER stress and reverses insulin resistance even in severely obese mice. We did learn, however, that the paper was recently accepted to Science and will be coming out shortly—maybe there will be more information then.

In other papers presented in the oral section, Dr. Mario Saad of the University of Campinas (Sao Paulo, Brazil) showed that mice with an inactivating mutation of TLR4 (a member of the toll-like receptor family) were resistant to diet-induced obesity, and maintained high metabolic rates, even after eight weeks of high-fat diet consumption. Bankim Bhatt, Ph.D., of the University of Pittsburgh, presented data from TLR4 knockout mice (no expression of TLR4 in any tissue), which showed that these mice were insulin sensitive. These data are similar to what Dr. Flier showed last year in his Banting Lecture. Apparently, there is quite a bit of competition in the field of toll-like receptors! Another highlight of the session came from a talk by Meredith Hawkins, M.D., of Albert Einstein University, where she presented some data that indicated some of the insulin-sensitizing effects of TZDs may come from reducing the amount of cytokine-producing macrophages that are found in fat.

PART SIX: POST-ADA CHATTING WITH JAY SKYLER

We were fortunate to sit down with Dr. Jay Skyler this week to hear his ADA impressions and to talk about other exciting developments in the field. A past President of the American Diabetes Association, Dr. Skyler is today a professor of medicine, pediatrics, and psychology at the University of Miami and associate director of the Diabetes Research Institute. Dr. Skyler's academic and clinical experience is vast, and he's a major figure on the global diabetes stage – in addition to being on the board of directors at Amylin and DexCom, and having been on the board of directors at MiniMed, before its 2001 acquisition by Medtronic, he sits on well over a dozen scientific advisory boards at various pharmaceutical and medical device companies throughout the U.S. and Europe. We have long admired Dr. Skyler's commitment to diabetes and were thrilled that he agreed to be the focus of our seventh in-depth DCU interview. We share highlights of the interview here and you can find the entire interview on our website at www.closeconcerns.com.

Kelly Close (KC): Thanks *so* much for talking to us. We're doing a post-ADA newsletter and wanted to get your thoughts on the meeting. What are your big picture take-aways? What did you think of the science and the products?

Jay Skyler: I was actually disappointed in the meeting, disappointed because I've kept up with all the new things in diabetes and therefore there was little or nothing new that I saw at ADA that I didn't already know about. You know, I like ADAs where I get some *really* exciting stuff. Maybe all that means is that I'm *too* close to things, because everybody else I know loved it!

KC: Let's talk about DPP-4 inhibitors a little bit, for a start. What did you think of Novartis' vildagliptin data?

JS: I actually thought that vilda [vildagliptin] did better than sita [sitagliptin] in A1c lowering in most of the abstracts. That's a hard thing to analyze because they start out at different points, making analysis tougher. And they're not done in the same population nor in the same country. The other thing that makes it hard to compare is that vilda was willing to go up against active comparators, and sita (until the very end) didn't go up against anything but placebos. And placebo's a pretty good straw man. Also, sita did all of its studies at QD (once daily), and vilda did most of its studies at BID (twice daily) and they did some studies that showed that you seemed to get a similar effect at BID as you do at QD for the same total amount, 100 QD versus 50 BID. So you can see it's really hard to make comparisons.

KC: So talk to us a little bit about what you think will happen. Do you think the drugs will be approved – with or without panel? Will they get reimbursement? Do you think patients will want to use them even though the drugs are weight neutral at best?

JS: You wouldn't think they're weight neutral if you read the press release!

KC: Trial design can be tricky to assess.

JS: There's only the one study that has showed a little bit of weight loss. I look at DPP-4 inhibitors fundamentally as weight neutral. It is really tough, as you point out, to show in a trial a drug that is basically weight neutral but to use it in a trial doing a diet and exercise program. I would have preferred to see the drug going just against a placebo there, because then you can figure out the real effects. My general impression from the totality of the data on DPP4s is that they are weight neutral. They are not weight loss, despite the press release that said otherwise.

KC: So on Byetta - everyone has a story about weight loss, but it's our sense that it was mostly endocrinologists who were talking about it.

JS: Yes, it's not been marketed very heavily outside of endocrinologists. By second quarter this year, it was already evident that there was going to be a potential shortage if it was expanded, so a broad PCP launch hasn't happened. The launch of Byetta went even better than was expected and they just had to hold back.

KC: Wow. Do you think that makes primary care doctors more excited to get it because they can't have it? If some PCPs do go straight to using DPP4s, and this assumes the reimbursement is there—then do you think that it will delay them from moving some patients to Byetta?

JS: Doctors always delay injectables. But once they get used to it, I think that they're going to want to have the weight loss effects of Byetta. And the patients are going to go nuts, they will be demanding it. That's where there is a real dilemma.

KC: What do you think about the company's decision to urge endocrinologists not to put new patients on Byetta right now?

JS: I don't think they have a choice. Ideally what you want to do is be able to keep your existing patients treated and you can't risk not having that be the case.

KC: There's a worry that part of the shortage is from too much off-label use of Byetta to treat obesity. What do you think about that?

JS: I don't think that's true. I just don't see much off-label use going on. And it's probably not a wise drug to use off-label in non-diabetic people because it causes glucose-stimulated insulin secretion. You may then over-secrete insulin and get hypoglycemic because you've already got endogenous insulin and you don't need to accelerate anything. There's also a theoretical danger because you would be altering gastrointestinal flow concurrently. You don't want to cause any late hypoglycemia, and that could theoretically happen in non-diabetic people taking Byetta.

KC: So one thing about Byetta, aside from weight loss, is that A1c's are definitely improving too. The question is, are A1cs improving more in real life because patients are more motivated or is it just the drug? What is your real-life experience?

JS: I think people are more motivated. My clinical experience has been that people who get on Byetta really get enthusiastic about their diabetes because they're losing weight and controlling their glucose at the same time, and they've never had that happen before. That gives them a high.

KC: That has to be excellent to see! What is it doing for doctors? To have a medicine that is motivating patients, that must make life a little different for them as well.

JS: I think doctors are thrilled with it too. It goes across the spectrum. And it's very different than anything we've had in the past because of that. Everything we've had in the past has been more of the same—this is clearly and distinctly different.

KC: What do you think the impact would be of TZDs on beta cell preservation? How do you think the average endocrinologist is thinking about TZDs right now? And how do you think about them?

JS: Well, you probably are aware that I am the antichrist for TZDs.

KC (laughing): Yes. Tell us about that.

JS: Well, it goes back to Rezulin. That was clearly a problem in terms of causing liver disease, and everybody else was enthusiastically supporting it and I couldn't figure out why. I developed the view we can treat diabetes and control glucose with insulin and don't need a TZD for glucose control. And why take a risk of liver disease when I don't need to? And so that's why I never started using Rezulin when everybody else was.

Now, I am the first to admit that the other TZDs are not Rezulin with its liver disease effects. The others don't have that, thank goodness. On the other hand, what the others do have as part of their mechanism of action is that you invariably will gain weight if the drug works. And my patients who have to buy new

clothes don't care whether it's a metabolically good drug. They care that they're buying new clothes. And so I've just never really seen a good argument for why TZDs ought to be used.

KC: So much of the focus with Amylin is on Byetta - did you see anything interesting about Symlin at the meeting?

JS: I thought it was nice that Symlin can be used without mealtime insulin. Lantus plus Symlin could be a really exciting play in the management of type 2 diabetes, controlling postprandial glucoses adequately while not having to worry very much about anything else.

KC: What about inhaled insulin? I know that you were pretty enthusiastic about inhaled insulin when it got approved. You know, it's six months later and it's about to be launched. What advice would you have for Pfizer? How do you think it will play? Do you think it will be reimbursed?

JS: Well, you've thrown out some of the $64,000 questions, for which I don't know the answer. The barriers to adoption of Exubera are several. One is reimbursement. What is it going to cost and where is it going to be reimbursed? Is it going to require prior authorization? All those things that add to the burden of reimbursement, and if a managed care company is looking at it, are they going to actually reimburse something where the only benefit is patient acceptability? That's one issue.

A second issue that is faced is who's going to schedule the pulmonary function tests—and who's going to pay for them? I don't think we know the answer to that, and logistically it is not easy.

KC: Why wouldn't Pfizer just say they would pay for it?

JS: Even if that happened, I think you face another set of problems because the recommendation is to perform pulmonary function tests at baseline, then every six months during the first year, and every year thereafter. And if each time it's done in a different lab and the technique is a little bit different and the value looks low, well, that might be a technical difference. How do you distinguish that, and interpret that adequately? Or do you mistakenly blame Exubera? I think that's a dilemma that they haven't quite thought through that they need to face.

The third issue is: how long will it take to teach somebody how to use the Exubera inhaler? Now if you just inhale, that's easy, but that's not the only thing you need to teach. You need to teach people how to take the device apart, how to change the transjector, and how to clean the device. And none of those things are either intuitive or easy. So that's another round of hurdles.

KC: Some want to see Exubera being used in a large population for a few years before they really make a decision about whether it's really safe. What did you see in the trials in terms of safety signals?

JS: There's always the potential that there are safety signals that you don't see, and there's no way to handle that except for over time, but time eventually will answer that. The question is should we be worried about that in this particular setting, and I am less worried about that here than I am in other places. I think that the one thing that we have learned is that there's a greater safety database here than there is for most other drugs. For example, I am more concerned about the DPP-4 inhibitors.

KC: Yeah, so let's talk about that. Can you outline the safety issues with DPP-4 inhibitors for us?

JS: DPP-4 the enzyme works on at least 62 known peptides. And that looks like a side effect waiting to happen because we don't know what lurks behind when the effects on some other peptide become manifest in some people. So I'm more worried about that than I am about Exubera, which I think we

know an awful lot about and which has been in very long-term trials relative to other products. So I am actually pretty confident Exubera doesn't have anything that we know about in this kind of timeframe.

KC: How important is tolerability for primary care doctors? You know, if the FDA approves the drug people generally believe that it's safe. So doctors may just generally believe that the inhaled insulin is safe, right? What about DPP-4 inhibitors?

JS: Well, tolerability seems great so far. There is no signal that I've seen talked about with the DPP-4s that suggest that there's any problem at all. I don't think that's a big deal at all for PCPs.

KC: Whereas the endocrinologists are more willing to work people through the first month or so of treatment.

JS: Endos want to do what's right and what sounds scientifically rational. PCPs want to do what's easy to implement and that is good for their patients. I think the one thing that people forget about sometimes is that most PCPs really care about what's good for their patient. That's what the business of being a doctor is all about. And so they really care about that and they listen to their patients. And so what happens is that if the patient in any way says that they're concerned about, say, injection in this case, they're going to walk away from it. And that's where I think Exubera has a great chance; it resonates with patients.

KC: We're curious what you thought about the competitive data on the GLP-1 front.

JS: The data on liraglutide continues to show what it's shown before. It still fails to have much impact on postprandial glucose. I'm not sure why that is, but it's probably got something to do with the magnitude of the effect. But as long as it continues to lack that impact it's going to get classified as a drug that doesn't quite compete.

KC: Byetta is being tested at both ends of the spectrum, in monotherapy and in combination with insulin. Which end do you think is more important to invest in?

JS: Both, but I think it's going to be used with insulin no matter what, so if I were investing, I'd invest in the monotherapy end and in the pre-diabetes component of it. That's where people will want to see more data. But I think both are important. I think that we have had in type 2 diabetes for the longest time, an insulin-o-centric viewpoint, then an insulin-resistance-centric point of view, which is probably too extreme in that direction. And I think that, from a therapeutic standpoint, we ought to be having a GLP1-centric point of view and more use, if they're safe, of DPP4 inhibitors. Going forward, treatment is going to be much more focused around the endocrine pathways. So I think it goes on both ends.

KC: Do you think that the DPP-4s should be used as a monotherapy or that we should use then in combination?

JS: My therapeutic paradigm over the last year has turned out to be that I start with metformin. If I fail to get adequate glucose control, I add Byetta. If I fail to get adequate fasting control, I add insulin-- for most of the year, it's been Lantus, now it's either Lantus or Levemir. And that works for the most part. So I've been very happy with that kind of scheme. And I haven't really needed to do anything else, whereas other people -- you know, the package insert says you can use Byetta in the presence of sulfonylureas and that's one of the places that they did the AMIGO studies. I personally stop the SFUs every time I start Byetta; I don't see any compelling reason to continue to give a drug that has weight gain and hypoglycemia associated with it when I can use a therapy that doesn't do those things. I wouldn't see any compelling reason to keep the SFUs on the market once the DPP-4s are available.

KC: There has been so much use of monotherapy in the past, even when the patients are failing in getting to goal. Do you think that's going to change?

JS: I hope it changes. I think that one of the things that's going to drive that a little bit is the availability of DPP-4s combined with metformin. Using DPP-4s plus metformin, you won't be putting in a component that has weight gain, you won't be putting in a component that has hypoglycemia, and you will be treating both defects of the disease. Hopefully that idea will get traction.

KC: Anyways, back to continuous – how about continuous in type 2?:

JS: You know why continuous is really going to win in type 2? We're going to go from now, where it's three and five days to seven days or 14 days so that we have a longer duration. We're going to eventually have one calibration for each sensor you put it in, and then the factory calibration. When we have factory calibration that can last for a week or so, it will be a whole lot easier to put on a DexCom sensor and leave it in place than it is to stick your fingers. And we're going to end up with people who will routinely be walking around with A1c's in the 6's instead of routinely walking around in the 8's and 9's. And that's going to really change the face of diabetes.

KC: Do you think that endocrinologists will start renting them and using the continuous monitors part-time for their type 2's?

JS: I think in the end, everybody will use it all the time because the patients will love it. With just sticking that thing in place and then being able to look at it without having to stick their finger anymore and knowing what they are continuously, and seeing what food does to blood glucose—everybody will want to do it all the time; nobody's going to give it up.

KC: We can't wait to see you next year in Chicago! Thank you *so* much again for your insights and for so much commitment to the field.

—ADA coverage by Dan Belkin, Leah Edwards, Katelyn Gamson, Aviva Gilbert, Cindy Glass, Erin Kane, Patty Pringle, Cullen Taniguchi, and Kelly L. Close

2. 2006 Annual JDRF Conference - Global Diabetes Research Forum

Seeking to accelerate the approval process of continuous sensors and – if completed – an artificial pancreas, the Juvenile Diabetes Research Foundation is talking to FDA officials to set concrete standards for future reviews and to answer agency experts' questions as they arise. The JDRF will also be working with Medicare officials and with private insurers to make coverage a priority.

The key for coverage is showing, through clinical trials, that these new technologies reduce A1c's as well as hypoglycemic incidents.

These were some of the highlights from the Annual JDRF Conference in May, which underscored the priority that the organization is now giving to the artificial pancreas. The JDRF announced earlier this year that it will spend $6.5 million for research on continuous sensors specifically and a "closed loop" system generally, which would tie sensors to insulin delivery in a partially or completely automated fashion. Such an artificial pancreas would rely on computer algorithms to calculate insulin doses.

At the conference, Dr. Aaron Kowalski, JDRF's Director of Strategic Research Projects, highlighted how very difficult tight control really is. His data showed that lower A1c's led to fewer complications but more hypoglycemic episodes. Studies using continuous glucose monitors also demonstrated that even

patients performing nine finger sticks a day spent only 30% of the day between 90 and 130, while another 30% of the day the numbers were over 180. Type 1 patients spent over two hours a day in the hypoglycemic range, usually during the night. Based on this data, Dr. Kowalski concluded that still better control is needed, and that's why the JDRF is finding research on the CGMs and the artificial pancreas itself.

Accurate CGMs would be a huge improvement over repeated finger stick measuring, for the monitors would indicate whether glucose levels are trending up or down. The FDA has approved three monitors to date: DexCom's STS Sensor, Medtronic's Guardian RT Sensor, and most recently Medronic's Paradigm REAL-Time Insulin Pump and Continuous Glucose Monitoring System, which was approved in April 2006, nearly half a year ahead of schedule. Abbott's Navigator Sensor is currently under FDA review, and we eagerly await word on what appears to be excellent technology, based on data reported at ADA (see the ADA postview above for more details).

A reliable CGM should be a key step toward an artificial pancreas. There is, however, disagreement about whether the approved continuous monitors perform with enough accuracy to be incorporated into a "closed loop" system of an external pancreas. The closed loop would link a monitor directly to an external insulin pump via an algorithm that tailored insulin dosage to the registered glucose trends. This proposed system is computerized and therefore requires an extremely reliable monitor for safety. At this point, none of the current continuous monitors has been approved as a substitute for finger sticks. On the flip side, the preliminary data presented at the JDRF meeting by Dr. Stuart Weinzimer, Associate Professor of Pediatrics at Yale Medical School, showed that even with first-generation algorithms, the closed loop provided significantly better control than the pre-trial levels.

Dr. Kowalski showed that using a continuous monitor with finger sticks did provide a more comprehensive picture than either measurement alone. A "hybrid loop" using CGM coupled to a manual pump was far superior to point-in-time only maintenance.

Current monitors, despite the evidence, still have not been approved for children and do not qualify for insurance reimbursement. Additional data confirming the monitors' efficacy will be needed.

In his remarks, Dr. Weinzimer laid bare the daunting challenge of an artificial pancreas. He posited that the first of two major steps toward the external closed loop would be developing a real-time glucose sensor that can be used 24/7 with downloadable data for retrospective analysis and insulin dosage adjustments. When connected to the currently available external pumps, the system could substitute for pancreatic function. Once this is achieved the second major step would be developing a real-time algorithm to mimic the fine adjustments of *in vivo* physiological insulin secretion. This algorithm would have to include the proportional, derivative, and integrative aspects of insulin dosage and would need to be fine-tuned for each patient. Insulin dosage would first be calculated to be proportional to the point-in-time glucose level. This dosage would be adjusted for the derivative, or rate-of-change, of the registered glucose trend. Both of these calculations would be in addition to the integrative, or slowly adapting, basal rate of insulin delivery.

In the closed loop system, sensor signals from the continuous monitor would be transmitted to a laptop computer that calculates the necessary rate of insulin delivery based on point-in-time and trend data. The rate of insulin delivery is then transmitted to the external insulin pump and released. Dr. Weinzimer provided data from a pilot clinical trial showing that the present prototypic technology while not yet ideal, still helps most people with diabetes achieve more tightly controlled glucose levels. In a comparison study of the first generation artificial pancreas, the five subjects who used a fully closed loop system had mean glucose level of 156, with nocturnal of 109 and peak postprandial of 232. In a follow-up study in which patients used continuous monitoring but manually controlled insulin pump dosage, patients

achieved a mean glucose level 135, with nocturnal 114 and peak postprandial 191. In this study, users initiated smaller "mini-boluses" prior to meals to try to blunt post-meal hyperglycemia while running the closed-loop algorithm in the background. Dr. Weinzimer emphasized that improving closed loop performance will require better algorithms as well as better sensing devices to address the issues of prandial control, reduction of nocturnal hypoglycemia, and adaptation of insulin delivery under dynamic conditions.

JDRF's work continues on both the technology and algorithms for an artificial pancreas as well as FDA approval and insurance reimbursement. We'll have to see what the updates are over the next few months – we'll be watching the JDRF website closely!

—By Jenny J. Jin and Kelly L. Close

3. Literature Review: The New England Journal on Food Marketing and Public Policy

Nestle M. "Food Marketing and Childhood Obesity – A Matter of Policy." N Engl J Med June 15, 2006. 354(24): 2527-2529.

Mello MM et al. "Obesity – The New Frontier of Public Health Law." N Engl J Med June 15, 2006. 354(24):2601-2700.

Marion Nestle, Professor of Nutrition, Food Studies, and Public Health at New York University, reported the results of the CDC's new Institute of Medicine (IOM) study entitled *Food Marketing to Children and Youth: Threat or Opportunity* in *New England Journal of Medicine* earlier this month. The study details how the marketing of foods to children has adversely affected children's health. Nestle's article is related to the health policy report by Mello et al. included in the same issue of *NEJM,* in which Mello, Studdert and Brennan discuss possible public health strategies for combating obesity.

The IOM study shows that the food industry intentionally targets children in its marketing of high-calorie, low-nutrient foods. American children spend $30 billion per year of their own money on junk food – never mind the amount their parents spend! Altogether nearly $10 billion per year is spent on marketing children's foods. After analyzing 123 published studies on the subject, the IOM concluded that this kind of marketing adversely affects children's appetite, diet, and weight, causing them to develop unhealthy eating habits. In other words, the advertising works: the children purchase unhealthy foods and they ask their parents to do the same.

Nestle warns that recent advertising has only become more aggressive as it moves beyond television to product placement, character licensing, celebrity endorsements, the Internet, and more. The most insidious campaigns convince children that certain foods are "just for them," making them believe that they and not their parents know best about their own diets. Parents can try to combat this by educating their children to think critically about food advertisements, but this is nearly impossible to do for younger children.

The IOM also strengthens the link between food marketing and diabetes. The prevalence of obesity in children aged 6-19 has gone up from only 4-5% four decades ago to 16% for the 1999-2002 period. If much or even some of this increase is due to uncontrolled food advertising, then curbing these marketing campaigns will slow the increase in type 2 diabetes.

In light of the IOM report, the U.S. government should more aggressively curb food advertising. The IOM writes that if the industry does not soon shift its marketing campaigns away from children, then "Congress should enact legislation mandating the shift."

In a related health policy report in this issue of *NEJM*, Mello et al. suggest public health laws to combat obesity. They begin by drawing parallels between this new frontier of obesity with other established areas of consumer health the government has historically regulated, such as alcohol and smoking. The authors argue that obesity is a valid target of public health law due to its proven cost to society. Mounting evidence of the link between junk food advertising and obesity (such as the IOM report) supports governmental regulations on food advertising.

At the state level, litigation and legislative measures have been taken against unhealthy food advertising.

- **Litigation faces hurdles** because obesity-related lawsuits have trouble proving the causality of their injury and that the danger was "not 'open and obvious' to the ordinary customer." Already 21 states have personal responsibility laws that prevent obesity-related lawsuits against fast food companies. Despite this, Mello et al. praise the publicity that obesity-related lawsuits bring to the cause.
- **Legislative measures have focused on creating more nutritious school meals, increasing physical activity, and preventing the sale of junk foods.** Outside of schools, some states have built more attractive exercise spaces or taxed junk food, though the latter is complicated by the blurred line between nutritious and non-nutritious foods.

At the federal level, the Federal Trade Commission (FTC), the courts, and the Food and Drug Administration (FDA) are the major players – and obstacles – in fighting obesity.

- **Because the FTC has authority over food advertising, it can regulate advertising to protect children.** However, historically its attempts to do so have failed for three reasons. Politically, the food industry wields too much money and influence. On a practical level the FTC has had trouble deciding what constitutes a children's audience, and food advertising has not been irrefutably linked to eating habits. Though TV tracking technologies and new evidence have now addressed the latter two problems, the authors are not sanguine about the FTC moving against traditional consumer freedoms.
- **Federal legislation is limited by First Amendment rights to free commercial speech.** Over the past three decades, the Supreme Court has been widening protections on commercial speech. The authors believe only strong evidence that food advertising is causing obesity will bring about regulations.
- **The FDA's control of food labels gives it the power to inform consumers, who generally value food-label information over advertisement information.** Studies suggest that consumers do use food labels to make healthier food choices. In recent years, the FDA has increasingly required more informative food labels. The agency, however, does not have that authority over restaurant food, which is exempt from labeling. Mello et al. argue that fast food restaurants should be required to have food labels as well. After all, chains like McDonalds have very standardized foods that would be easy to label.

The government needs to counteract bad advertising with good advertising. Until more concrete evidence demonstrates the harm of food advertising, enacting government regulation will be difficult. In the meantime, the authors suggest counter-advertising to combat industry advertising. Instead of limiting information flow, the government should develop campaigns about food education in schools and elsewhere. These may be easier to implement while raising fewer constitutional concerns. Regardless, any advertising-restriction strategy must be coupled with a food literacy and education program if consumers are ultimately to make the right choices.

—By Jenny J. Jin

4. Book Review: *What to Eat* Marion Nestle, PhD, MPH. 611 pages, North Point Press, 2006. $30.00/$39.95 CAN

After our interview with Marion Nestle last month and the publication of her recent editorial on food marketing to children in the *NEJM*, we were very excited to gain a more in-depth look at her work by reading this, her latest book. *What to Eat* is certainly well worth reading, and not just for people with diabetes. A delightfully lucid writer, Dr. Nestle's conversational yet authoritative voice rolls smoothly off the pages with nary a sentence of tedium or extra information.

It's clear from the onset that Dr. Nestle is not just another fad dietician out to promote her dietary regimen . As she tells us in the introduction, "This book is about how to think about the food you eat." She wants the average American consumer to learn enough to make informed choices in the vast quagmire of confusion that nutrition has become. This is why she began her research for the book not with pursuing abstract studies and reports, but by putting herself in the consumer's shoes and visiting supermarkets – a vast number of them. Along the way she made endless measurements and calculations, took food samples for laboratory analysis, and went on to peruse reports and talk to clerks, managers, executives, farmers, inspectors, and scientists, to list just a few. In the process she gets to the bottom of every major issue in food that we as consumers should (but usually don't) know more about.

Though Dr. Nestle is no dogmatic preacher, she does dispense advice about eating. The difference is that instead of warning and ordering us about eating this or that, she appeals to our common sense, laying out both sides of the argument on contentious issues like organic foods and artificial sweeteners before she tells us her opinion on the matter. We end up getting the sense that her advice is probably worth taking, but we're offered enough information to make informed choices even if they differ from hers. And the breadth of information that she covers is exhaustive. In the spirit of her research approach, she models the chapters of this book along the lines of a journey through the aisles of a typical suburban supermarket. Every major food group gets discussed in the process, beginning with staples such as produce, dairy, meat, and fish and moving on to the more dangerous territories of frozen foods, processed foods, and beverages.

For the casual reader, this encyclopedic approach may be a little too much to handle – after all this is a very long book, even if it reads quickly. Fortunately, Dr. Nestle seems to have anticipated this possibility and chose to highlight some of her more interesting and important quotes in the gray text boxes that appear in the margin every few pages or so. These include such gems as her central advice on food and health: "The basic principles of good diets are so simple that I can summarize them in just ten words: *eat less, move more, eat lots of fruits and vegetables*. For additional clarification, a five-word modifier helps: *go easy on junk foods*." This is simple advice indeed, though if it was simple to follow so many Americans wouldn't be suffering from obesity. The economic and political reasons why Americans have so much trouble following it is one of the recurring themes of this book.

Simply put, most major food companies care everything about profit margins and market share and almost nothing about environmental or economic sustainability – never mind consumer health. Because these companies make so much money, they have a lot of economic and political power to wield and they use it to hamper safety advice and regulations whenever they can. Their lobbyists in Congress ensure that it is nearly impossible for the FDA or any other regulatory agency to ever tell consumers to eat less of something, no matter how detrimental that food may be to their weight and health. New labeling requirements, safety regulations, and dietary advice about restraint and moderation is endlessly delayed by congressional order (donations, mm!) and what should be straightforward advice gets hopelessly muddled by qualifiers in the process. A striking example given is the U.S. Dietary Guideline for Sugar, which has morphed from a no-nonsense "Avoid too much sugar" in 1980 to the awkward 2005 advice to "Choose and prepare foods and beverages with little added sugars or caloric sweeteners, such as amounts

suggested by the USDA Food Guide and the DASH [Dietary Approaches to Stop Hypertension] Eating Plan." This beautifully incomprehensible sentence came into its present form after industry efforts pushed the original guideline through three other increasingly wishy-washy incarnations.

This entire theme of food company irresponsibility brings up one of the book's few weaknesses, if it can even be called that. Because its organizational principle is food group based, some of the more pervasive issues in food and health that Dr. Nestle examines – like food company policies, calorie counting, health claim advertising, and organic labeling – don't have chapters of their own. Rather, they get discussed throughout the book as they relate to specific food categories. Others are simply randomly placed, like the digression on calories and diets sandwiched in the frozen foods section between chapters on decoding ingredients lists and carbohydrate absorption..

All of this just barely skims the surface of what Dr. Nestle covers in *What to Eat*. As we noted, one of the best qualities of this volume is the comprehensive background and multifaceted treatment given on each major food choice that we as consumers must make. Only by reading it will you be able to appreciate the full level of detail and care that went into this book – go to it, and take it to the beach!

—By Jenny J. Jin and Kelly Close

4. Upcoming Conference Preview (fees go up after June 30 for both EASD and IDF

- **AADE, August 9-12, Los Angeles, CA www.aadenet.org**
  Our favorite meeting every year to find out what patients are really thinking. The conference will feature over 100 educational sessions on areas such as models of chronic care, health care management programs, and diabetes self-care. Additional topics include women's issues, prevention, obesity, disaster preparedness, etc. See the schedule and our sense of the highlights at www.closeconcerns.com.
- **EASD, September 14-17, Copenhagen, Denmark, www.easd.org**
  A preliminary draft program in PDF format is now available at www.closeconcerns.com. ; EASD promises a wide variety of topics in both basic science and clinical care, including genetic prediction of diabetes, transcriptional and regulatory factors in glucose maintenance, treatment of complications, and closing the loop on an artificial pancreas. As noted, 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's purpose was to determine if ramipril and/or rosiglitazone would prevent the onset of type 2 diabetes, and this study has been highly awaited.
- **IDF 19th World Diabetes Congress, December 3-7, Capetown, South Africa, www.idf2006.org**
  Another long-awaited trial, ADOPT (which compares rosiglitazone monotherapy with metformin or glyburide/glibenclamide in disease progression, beta-cell function or risk markers for macrovascular complications in recently diagnosed type 2 patients) will be presented here. This and then, the wine – it's hard to say no, isn't it?! The advance program with a list of lectures, symposia, exhibitors, and registration info can be downloaded at www.closeconcerns.com.

—By Jenny J. Jin and Kelly L. Close