DIABETES CLOSE UP

Diabetes Close Up
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DCU ADA 2005 Download

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

From the Editor: What an outstanding ADA! The best in years. Much excitement swirled for us, particularly on the drug front – we were blogging nightly (see www.closeconcerns.com for evening updates) over select interesting findings and snippets. While we'd not position this issue as anything close to a complete download[1], our issue does contain many of our ultimate meeting highlights. Someone asked on Day Four what the most excitement elements of ADA were. For us, "EDIC, EDIC, EDIC; Symlin; really earlier, more aggressive therapy, everything physiologic; new Van den Berghe hospital data; beta cell preservation/regeneration … " A year ago, we would have thought that this would've been the device meeting of the year – but we did a double-take. That'll be next year, we would hope. **The** ***most important finding? Without a doubt we were most enthused by the EDIC data showing that early, intensive glucose control significantly reduces macrovascular events in type 1s. Legions of clinical implications here (see below). Although several people asked essentially what the big deal was since it was "expected," we believe it is absolutely critical that payors, providers, and patients now have evidence – overwhelming evidence! – that for type 1 patients (and of course where type 1s go…) any therapy regimen that's not intensive needs to be thrown out the window and whatever we can do to get to people on the intensive track safely must be more aggressively pursued. Onward!***

–by Kelly L. Close

[1] There are many sessions we'll save for Diabetes 2005, to be published in August – i.e., the terrific pump session, many of the symposia, our fabulous lunch with Michael King and Drs. Irl Hirsch and Wendell Cheatham, the hospital data, details on beta cell regeneration …

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

1. ADA issue – One ADA, a zillion interesting elements. Selected highlights from ADA ...

LATE-BREAKING NEWS ON TRIALS

Muraglitazar Data
Dr. David Kendall (Chief of Clinical Services and Medical Director of the International Diabetes Center and Associate Professor of Medicine at the University of Minnesota Medical School, Minneapolis) reviewed previously* released data on BMS/Merck's muraglitazar before disclosing new results. (*See the May 2005 *DCU* for a report on the AACE meeting held in DC.) The full clinical data are still under review, but Dr. Kendall was able to discuss muraglitazar in quite good detail.

A pre-planned open study of the durability of effectiveness of muraglitazar involved 157 patients who had been in the 5 mg dosage group during the dose-ranging study (36 subsequently withdrew from the study, and 33 couldn't achieve adequate glucose control on 5 mg). Successful patients on 5 mg muraglitazar went from an average A1C of 8.0% to an average of 6.5% percent by week 24 of the trial and maintained that level of control out to two years. These results were characterized as significant due to muraglitazar's potential for a slowing-down effect. Dr. Kendall referred in his presentation to the theory that tight glycemic control might have beneficial effects on beta cell health in people with type 2 – we'll be staying tuned on this.

Dr. Kendall reported on an additional muraglitazar study, where the drug was evaluated in 1,159 patients with type 2, all of whom were taking metformin. All continued to take metformin but were randomized (double-blind) to take either 5 mg muraglitazar or 30 mg pioglitazone (Takeda's Actos) once daily in combination therapy. After 24 weeks, the muraglitazar group's A1C fell by 1.1 vs. 0.9 (absolute change) for the pioglitazone group. That didn't seem like such a necessarily big change (we didn't catch the baseline or it wasn't given, we're not sure), but the differences in lipids were greater for muraglitazar vs. pioglitazone, with triglycerides reduced by 28% vs. 13%; HDL up by 19% vs. 14%; non-HDL-C (LDL plus cholesterol contained in triglyceride-rich lipid particles) lowered by 6% vs. 1%. Also of interest, apo B (a protein found in lipid particles) went down by 12% in the muraglitazar group compared to a 6% reduction in the pioglitazone group. In the muraglitazar group, Dr. Kendall said, 8-11% of patients discontinued therapy because of treatment related adverse events, compared to 5% of the pioglitazone group. BMS seemed to be pushing the theme about better lipid and glycemic control reducing cardiovascular disease.

The most common side effects seen in the trials were bilateral pitting edema (5–8 % of durability study participants) and weight gain of 2 to 10 pounds over 52 weeks. However, the edema was highly dose-dependent: in the dose-ranging study, fully 40% of the group taking 10 mg muraglitazar had developed edema. Though edema can be observed in many older, generally unfit type 2 patients no matter what their therapeutic regimen, a margin of up to 35% (40% minus 5%) is not easily explicable by anything other than the drug. It's unfortunate that the dose-ranging study data shown first at the AACE meeting indicated that although 69% of patients on a 20 mg dose of muraglitazar reached an A1C ≤6.5% by 24 weeks, that same group had a 45% rate of treatment-related adverse events. The 5 mg group, by contrast, showed 43% of takers reaching an A1C ≤6.5% by 24 weeks, with 22% exhibiting treatment-related adverse events.

Are we excited about muraglitazar? Well, we've just devoted about 600 words to it on this page and there's more to read in our Drug Update, so we are not unexcited, *per se*, at learning more about the results and we certainly are pleased by the prospect of more options for type 2 patients. But we wouldn't

say we were *convinced* by any stretch and we wonder about TZD competition. The big hurdle, FDA approval, must still be cleared. Then, in this post-Rezulin, post-fen/phen, post-Vioxx era, muraglitazar must face the most decisive trial of all: Phase IV.

Retinopathy in Recently Diagnosed Type 2: Doesn't Look Good

Dr. Richard F. Hamman (Professor and Chair, Department of Preventive Medicine and Biometrics, University of Colorado Health Sciences Center, Denver) presented "Retinopathy in Recent Onset Diabetes and Persons at High Risk of Diabetes in the Diabetes Prevention Program," which revealed that a very high number of patients have retinopathy at the time of their diagnosis of type 2 diabetes or develop that complication within a few years of their diagnosis. Even more worrying, patients who are not technically diabetic by the current diagnosis criteria may have early-stage retinopathy.

These data are highly relevant to the implementation of broader screening programs for type 2 diabetes and the necessity to develop more sensitive and specific diagnosis criteria and testing techniques than are currently available, as well as *reimbursement* for such.

Clearly, if people with type 2 diabetes have had hyperglycemic excursions (if not persistent hyperglycemia) for such a length of time that retinopathy has developed before their formal diagnosis, we are not detecting type 2 diabetes (or at least hyperglycemia) soon enough.

What's Good For the Eyes is Good For the Heart

Dr. David Nathan, Director of the Diabetes Center at Massachusetts General Hospital in Boston, presented extremely compelling data related to heart health in people with type 1 diabetes: Data from the Epidemiology of Diabetes Interventions and Complications (EDIC, a.k.a. the DCCT follow-up) study shows that tight blood glucose control is key to preventing heart disease. Dr. Nathan presented evidence showing that intensive diabetes management with **tight blood glucose control can reduce the risk of cardiovascular disease in people with type 1 diabetes by up to 57%.** According to the new data, every 1% reduction in A1C is correlated with about 20% reduction in cardiovascular risk.[2] Check *that* out. Way to make some type 1 patients gleeful …

The newly released EDIC data reported by Dr. Nathan showed that patients whose A1C levels were about 7% for six-and-a-half years during the DCCT had a 57% reduction in fatal and nonfatal heart attacks and strokes compared to patients whose A1Cs had been near 9% in the same time frame *even if their A1Cs went up after the conclusion of the DCCT*. Strikingly, 33% of the tight control group had taken statins, compared to 34% of the conventional group. Thus, *statin use cannot explain the difference in heart disease risk between the two groups*. We find this revelation absolutely crucial. Why, just a few months ago at Diabetes UK we heard British cardiologists and diabetologists arguing that all type 1s over the age of 25 ought to be put on statins because there was no evidence that glycemic control was implicated in the prevention of heart disease compared to statin use!

The phenomenon wherein a period of tight control has long-term benefits, which was first described in connection with the DCCT results concerning microvascular complications, is often called "metabolic memory." It is not yet known how long the positive effects of metabolic memory persist when diabetes control becomes less intensive; as a result, more and more healthcare professionals advise type 1s to strive for the best degree of glucose control that they can achieve without frequent episodes of severe hypoglycemia.

[2] Nathan, "Effects of Intensive diabetes Management on Cardiovascular Events in DCCT/EDIC." Late-breaking clinical trials. ADA 65th Scientific Sessions and Annual Meeting, June 12, 2005.

The DCCT results, released in 1993, showed conclusively that tight control of blood glucose levels in people with type 1 diabetes could prevent or delay the development of microvascular complications (retinopathy, nephropathy, and/or neuropathy) up to 76%. This data for the first time shows that the impact of tight blood control is also critical for macrovascular complications – very important for payors to take in, in particular, as now there is no way they can't support intensive therapy.
The ADA notes that type 2 diabetes increases one's cardiovascular risk two- to four-fold compared to someone who does not have diabetes (note we didn't say "a normal person"!).[3] The Centers for Disease Control and Prevention (CDC) have documented that in 2003, 28% of Americans with diabetes aged 35-64, 48% of Americans with diabetes aged 65-74 and nearly 60% of Americans with diabetes aged 75 years or older had cardiovascular disease.[4] While the EDIC findings are directly relevant type 1 diabetes, we believe they may ultimately be shown to have implications for type 2. Certainly, we know that tight glycemic control is not detrimental to heart health! We are not forecasting any drastic downturn in the sales of statins (estimated at a cool $15 and $26 billion, respectively, in the US and globally), particularly in view of the compelling Heart Protection Study, but we do anticipate that interest in tight glycemic control will continue to mount and will become more impossible to ignore.

DCU'S ADA DRUG UPDATE – THE PAUSE THAT REFRESHES

- **We published a DCU before last year's ADA in which we covered the "Generation 2005" drugs and in which Stephen Simpson flagged potential carcinogenicity in the dual PPAR class that ultimately slowed that whole class right down later in the summer – and we're updating it here with general notes on categories and leading drug targets for commercialization**. Yes, our eyes are still on all of these balls, so all that need a primer, read on for our best take at characterizations and regulatory estimates...
  - GLP-1 mimetics
    - GLP-1 mimetics replicate the enhancement of glucose-dependent insulin secretion and other antihyperglycemic actions of incretin hormones. Incretin hormones are released in greater amounts in response to oral glucose consumption than they are released in response to IV glucose. GLP-1 mimetics must be injected.
      ADA update on class
    - Amylin's Byetta (exenatide): FDA approval granted April 29, 2005
    - Novo Nordisk's liraglutide (NN2211): Phase 2b study initiated in January 2005; phase 3 expected to be initiated towards the end of 2005
    - Conjuchem's DAC™:GLP-1 (CJC-1131): In mid-April 2005, the company announced Phase 2 clinical trial that evaluated the Company's proprietary compound DAC™:GLP-1 to treat type 2 diabetes in combination with metformin. Conjuchem also announced that an ongoing Phase 1 trial identified a lead diluent for DAC™:GLP-1.
  - DPP-IV inhibitors
    - DPP-IV inhibitors block the degradation of the incretin hormone GLP-1 by the enzyme DPP-IV, thus extending the half-life of GLP-1 so that it can exert important glucoregulatory effects within the body. DPP-IV inhibitors are oral agents.
      ADA update on class
    - Novartis's vildagliptin (LAF-237): Phase 3 trials on-going
    - Merck's sitagliptin (MK-0431): Phase 2 data announced at ADA 2005
  - Dual-PPAR agonists
    Dual-PPAR activators belong to a new class called glitazars, which activate PPAR gamma lowering plasma glucose and free fatty acid concentrations and PPAR alpha lowering plasma triglyceride concentrations and increasing HDL cholesterol. Fibrates such as the cholesterol-

[3] *Diabetes Care* 2004; 27(Suppl 1): S68–S71.
[4] http://www.cdc.gov/diabetes/statistics/cvd/fig4.htm

lowering agents fenofibrate and gemfibrozil are currently available PPAR-α agonists and PPAR-γ is activated by thiazolidinediones (TZDs), a class presently comprised of rosiglitazone (GSK's Avandia) and pioglitazone (Takeda's Actos). Combining the effects of both drug classes into one therapy has the potential to create a monotherapy pill for type 2 diabetes, long considered a holy grail of type 2 diabetes treatment. However, the potential for tumors that this class has shown in rodents has created serious safety concerns in the minds of regulators and clinicians. Too, creatinine elevation concerns were voiced. Because of safety concerns several agents that reached Phase 1 and Phase 2 studies have been dropped before reaching Phase 3, including ragaglitazar (Novo Nordisk/Dr. Reddy).

ADA update on class

- Bristol-Myers Squibb's Pargluva (muraglitazar): in Phase 3
- AstraZeneca's Galida (tesaglitazar): in Phase 3, submission expected 2007

- ECRBs
  - The endocannabinoid system is involved in central and peripheral regulation of energy balance and possibly also smoking behavior. The theory is that cannabinoid receptors (the same receptors that bind tetra hydro cannabinoid [THC], found in marijuana) are responsible for increased hunger. Blocking these receptors is thought to decrease feeding behavior. Thus, endocannabinoid receptor blockers (ECRBs) are a potentially critical therapeutic class.
  - Given their role in food and smoking desire, it is currently speculated by some that ECRBs may have a role in alcoholism treatment or treatment for other forms of addiction, but no data is available on those potential uses. At NAASO last fall in Las Vegas, it was speculated that Acomplia would be a treatment for gambling. We daresay it won't likely be the first indicator the company pursues – that question is a hard one, though. Recently, we saw language about Acomplia "also" treating smoking – that was interesting to see smoking as an indication take more of a back seat.

    ADA update on class
  - Sanofi-Aventis's Acomplia (rimonabant), the first selective endocannabinoid type 1 receptor blocker: Phase 3
  - Compelling data, though disturbing CNS side effects in some trials - if you were about to note that many overweight/obese people are depressed, we might politely urge less generalization but would also point out that all patients w/ prior history of depression/anxiety or currently taking SSRIs were excluded from RIO studies, making quantification, um, difficult
  - Indication is the key question right now – could they get a diabetes indication? We don't think it will be the first indication by any stretch
  - At the AACE meeting in Washington, DC, in May, Dr. Louis Aronne said in a Sanofi-Aventis corporate sponsored symposium that at least six companies are at work on ECRBs, but none of them other than Sanofi-Aventis discussed them at ADA. At a dinner with Dr. Aronne at ADA, we heard him discuss some intriguing cocktails – that made us wonder about Byetta and Rimonabant, a potential combo on which some wanted to bet their house …
- Metabolex compound MBX-102
  - Metabolex's MBX-102, a.k.a. metaglidasen is a second-generation, non-TZD insulin sensitizer. The target profile of lowering glucose, lipids, and uric acid while avoiding weight gain and edema differentiates MBX-102 from TZDs. Avoiding weight gain and edema! Wow.
  - Currently completing Phase 2 clinical trials; expects Phase 3 to begin early next year
- Inhaled insulin
  - Since a German journal article on the concept first appeared in1925, inhaled insulin has resurfaced as a potential therapy for diabetes approximately every decade, according to Dr. Jay Skyler. The lungs represent an attractive site for insulin delivery because they offer a huge absorptive area for inhaled therapeutics, nearly the size of a flipping tennis court. Thus, most inhaled insulin formulations rely on pulmonary insulin delivery, though some strategies for

intranasal and orally absorbed insulin (Generex's Ora-lyn, now approved in Ecuador – yes, we thought that too! Ecuador?!) have also been explored.

- In clinical trials, inhaled insulin has tended to show similar efficacy to subcutaneously injected human Regular insulin, except in the case of MannKind's Technosphere insulin, which appears to have an onset of action close to that of – maybe better than? - Humalog and a duration of effect similar to that of human R. Diabetes control is generally not improved in patients who were already taking subcutaneous insulin, but insulin-naïve patients tend to see improved blood glucose control – sponsoring companies love these insulin-naïve studies, where improvements from A1Cs of 11 aren't so hard to show. Studies *have* shown that insulin-naïve patients are said to often prefer inhaled insulin to injections when they are given the option. At present, <30% of type 2 diabetes patients in the US are on insulin therapy. Inhaled insulin has the potential to meet a great unmet need: The average A1C in the US is ~9% and this could change significantly, resulting in better outcomes, if more type 2 patients took insulin. However, safety concerns are still an issue at present: questions over long-term impact on lung function, the potential clinical relevance of insulin antibody formation, the reliability of dosing dependent on patient technique, and the potentially tumorogenic implications of delivering insulin (that can spur mitogenesis) into the lungs, and the more effective insulin absorption seen in smokers (which could increase hypoglycemia) remain areas of concern among clinicians.

  ADA update on class

- Pfizer/Sanofi-Aventis's Exubera was filed at the FDA earlier this year
- Lilly/Alkermes' Human Insulin Inhaled Powder (HIIP) is in Phase 3
- MannKind's Technosphere Insulin is in Phase 3 (European trials)
- Novo Nordisk's AERx's iDMS (insulin Diabetes Management System) is in Phase 3
- Kos Pharmaceuticals' inhaled insulin is in Phase 3

- Drugs for microvascular complications
  - Drugs for diabetic microvascular complications (DMC) are now approaching the status of a class – very unmet need, so this is good. While ACE-inhibitors have been used to treat diabetic nephropathy for several years, they aren't specific compounds with indications for diabetic nephropathy. Stay tuned on this front.

    ADA update on class

  - Lilly's Arxxant (ruboxistaurin), a PKC-β inhibitor, is in Phase 3
  - Lilly's Cymbalta (duloxetine), an SSRI, was approved by the FDA both for depression and for relief of pain from diabetic peripheral neuropathy in September 2004
  - Throughout the European Union, duloxetine for depression and diabetic peripheral neuropathy is marketed by Lilly under the brand name Cymbalta and by Boehringer Ingelheim under the brand names Cymbalta in Greece, Italy and Spain, as Xeristar
  - Under the brand name Yentreve, duloxetine is indicated outside the US (but not approved by the FDA) for the treatment of stress urinary incontinence in women
  - For stress urinary incontinence, duloetine is jointly co-promoted throughout the European Union by Lilly and Boehringer Ingelheim under the brand name Yentreve, except for Greece, Italy, and Spain, where it is marketed under the brand name Yentreve by Lilly and Ariclaim by Boehringer Ingelheim
  - Pfizer's Lyrica (pregabalin) was approved by the FDA in December 2004 for the treatment of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia. Lyrica was approved by the FDA as an adjunctive treatment for partial epileptic seizures in adults on June 13, 2005

- Companies
  - Amylin – Byetta and Symlin
    - Byetta 82-week data and 2 year data was impressive – flatline A1C improvements at 1.2 percent and progressive weight loss. Quite interesting weight quartile data showed two big

things to us: 1) the top quartile lost 26 lbs and dropped A1C 1.8 points; 2) the bottom two quartiles who lost the least amount of weight still had 1.0 drop in A1C.

- Data in the head to head Lantus trial showed about the same drop in A1C but significantly more weight loss for Byetta (~nine pounds in absolute difference) ~importantly, we think Byetta is substantially easier to use. This matters hugely.
- Byetta publicity was fantastic. With a Byetta logo-emblazoned shuttle bus, bright orange and green beach-ready tote bags, and several symposia and scientific sessions devoted to it, Byetta appeared the most intensely promoted therapy of the meeting. Every single endo must want a patient on this drug – how can they stay in conversations with other endos and PCPs, otherwise?
- Symlin was undoubtedly the "sleeper" drug of ADA 2005 (for more on this drug, see our March DCU, *The Excitement Called Symlin*. We can't help it – we're very excited about this drug - some patients glowingly described in informal conversations how much better they feel since starting it. Amylin appears to be launching the drug slowly, to ensure proper HCP education, but we think some patients may want to skip the education – never a good idea. Although the drug doesn't cause hypoglycemia, hypoglycemia can ensue if insulin isn't reduced correctly. Since reactions vary by patient, it is not that easy to determine dosing combination (Symlin/insulin) from the outset. We believe Symlin will prompt more interest in physiologic therapy of all kinds. It will be interesting to see the impact of Symlin on type 2s on insulin - the AC137 for obesity study results are highly anticipated and should emerge around year-end.
- The possibilities of off-label use for both Byetta and Symlin arose frequently, as did potential combination therapy. We personally hope for a mix of insulin and Symlin though we're not sure about ph levels. We believe there is already some off-label use for Byetta – how could there not be?! We would expect less for Symlin early on since the complexity of the therapy is much higher, but patient interest in off label use will undoubtedly increase as patients hear more about both drugs. Clearly, interest in weight-loss properties of the drug are high. Obviously companies are decidedly not urging off label use.
- Yes, interest in combination therapy is high for Byetta – combining it with TZDs (there's a trial ongoing now), combining with insulin, combining with Symlin. Even more strikingly, at least one leading clinician forecast combination therapy for type 2s involving DPP-IV inhibitors (though no drugs in that class have yet been approved) and Byetta. Of course, we "stand aside" on that one. With an agent to control lipids and one for blood pressure, perhaps early- to middle-stage type 2s could enjoy normoglycemia and reduced cardiovascular risk; it will be interesting to see how trials evolve. Now that it has one label, we will clearly look to see more research on this drug. There is likely already intense investigator interest as well though the company has not commented on this. We personally are most excited about the combination of Lantus and Byetta. It's perfect – all the great stuff about GLP-1, plus basal coverage, plus no weight gain.
- Beta cell regeneration? In early 2004, Amylin announced a beta cell regeneration trial that the NIH is conducting in type 1 patients – we don't hear anything about this trial lately, but the results will be closely watched.

<u>Byetta posters</u>

- "Comparison of Exenatide and Insulin Glargine in MET and SU-Treated Patients with Type 2 Diabetes: Exenatide Achieved Equivalent Glycemic Control, with Weight Reduction and Less Nocturnal Hypoglycemia" (9-OR)
- "Improvements in Cardiovascular Risk Factors Accompanied Sustained Effects on Glycemia and Weight Reduction in Patients with Type 2 Diabetes Treated with Exenatide for 82 Weeks" (16-OR)
- "Exenatide Pharmacokinetics in Patients with Mild to Moderate Renal Dysfunction and End Stage Renal Disease" (469-P)

- "Exenatide (Exendin-4) Reduced A1C and Weight over 82 Weeks in Overweight Patients with Type 2 Diabetes" (477-P)
- "Mathematical Modeling Shows Exenatide Improved Postprandial B-Cell Function in Patients with Type 2 Diabetes Treated with Metformin or Metformin and Sulfonylurea" (482-P)
- "Exenatide-Induced Reductions in A1C and Body Weight in Long-Term Trials Are Not Explained by Gastrointestinal Side Effects" (485-P)
- "Insulinotropic Action of Exenatide (Exendin-4) Abates during Hypoglycemia in Rats" (523-P)

  <u>Symlin posters</u>
- "In an Open-Label Clinical Study Pramlintide Lowered A1C, Body Weight, and Insulin Use in Patients with Type 2 Diabetes Failing To Achieve Glycemic Targets with Insulin Therapy" (48-OR)
- "The Role of Subcutaneous Pramlintide Infusion in the Treatment of Adolescents with Type 1 Diabetes" (447-P)
- "In an Open-Label Clinical Study Pramlintide Lowered A1C, Body Weight, and Insulin Use in Patients with Type 1 Diabetes Failing To Achieve Glycemic Targets with Insulin Therapy" (478-P)
- "Perceptions of Patient Satisfaction during the Placebo-Controlled and Open-Label Phases of a Study in Patients with Type 1 Diabetes Treated with Pramlintide" (2091-PO)

- AstraZeneca
  - Galida (tesaglitazar) was not much discussed, which was a surprise to us after seeing the abstracts of the posters (below) in advance of the meeting. With such an aggressive research program, one would have thought that Galida would have been worked into the program in some way during its corporate-sponsored symposium "Metabolic syndrome: the perfect storm in vascular disease," but Galida was not mentioned despite the implications for metabolic syndrome apparent from the titles of the abstracts that AstraZeneca submitted to the ADA this year. Perhaps AZ is taking a tactic practically the opposite of BMS/Merck's with regard to muraglitazar: that is, AZ is quietly showing interesting, solid data about its drug and not counting chickens before they are hatched. This seems like a good idea. Galida creatinine elevations appear a concern and perhaps represent one reason behind absence of wide discussion.

    <u>Tesaglitazar posters</u>
  - "Tesaglitazar Improves Glucose and Lipid Abnormalities in Patients with Type 2 Diabetes" (83-OR)
  - "Tesaglitazar (GALIDA™) Improves Postprandial Lipid Handling and Glucose Tolerance in an Insulin-Resistant, Non-Diabetic Population" (614-P)
  - "Tesaglitazar Reduced the Prevalence of Metabolic Syndrome and Impaired Fasting Glucose in an Insulin-Resistant, Non-Diabetic Population" (615-P)
  - "Tesaglitazar, a Dual PPARA/Γ Agonist, Reduces Atherosclerosis in APOE*3Leiden Transgenic Mice" (956-P)
  - "Tesaglitazar Improves Apolipoprotein Abnormalities in an Insulin-Resistant, Non-Diabetic Population" (972-P)
  - "Lack of Pharmacokinetic Interaction between Tesaglitazar and Glibenclamide in Healthy Male Volunteers" (2145-PO)
  - "Lack of Pharmacokinetic Interaction between Tesaglitazar and Metformin in Healthy Male Subjects" (2146-PO)
  - "A Population Pharmacokinetic Analysis of Tesaglitazar in Patients with Manifestations of Insulin Resistance" (2199-PO)
- Bristol-Myers Squibb/Merck
  - At the ADA, Merck launched the brand name and logo for Pargluva, the compound previously known only as muraglitazar

- The booth was a Pargluva booth, not a BMS/Merck booth, with Pargluva's name and color scheme (purplish maroon and orange) displayed more prominently than either company's logo or colors
- There were no brochures or leaflets on display, which was not surprising as it is not approved. When asked for information, reps directed booth visitors to queue for a personalized Pargluva fountain pen. The queue was never very short.
- The Pargluva booth also offered telephones for visitors to use to phone home *gratis* and several computer terminals for free e-mail access.
- The public launch of the brand name Pargluva may be premature (that the compound won't need a brand name unless the FDA actually approves it), but we must give credit for ingenuity where credit is due: in an age of meaningless but cool brand names for drugs (i.e., Starlix) Pargluva calls to mind the words "dual-PPAR" and "glucose" in the same way that Byetta invokes "beta cells."

  Muraglitazar posters
- "Improvement of Glycemic Control with Muraglitazar, a Novel Dual PPAR A/Γ Agonist, in Combination with Metformin in Patients with Type 2 Diabetes: A Double-Blind, Randomized, Pioglitazone-Controlled Study" (14-OR)
- "Long-Term Treatment of Young Prediabetic db/db Mice with Muraglitazar, a Novel Dual PPAR A/Γ Agonist, Prevents Hyperglycemia and Preserves Pancreatic B-Cell Function" (269-OR)
- "Glycemic Efficacy and Safety of Muraglitazar, a Novel Dual PPAR A/Γ Agonist, Plus Glyburide in Patients with Type 2 Diabetes Failing Sulfonylurea Monotherapy: A Randomized, Double-Blind, Placebo-Controlled Study" (518-P)
- "Effects of Age and Gender on the Pharmacokinetics of Muraglitazar, a Novel Dual PPAR A/Γ Agonist under Investigation for the Treatment of Type 2 Diabetes" (519-P)
- "Glucose Lowering in db/db Mice Treated with Muraglitazar (a Novel Dual PPAR A/Γ Agonist) Is Not Associated with Changes in Hematocrit, Heart Weight, or the Renal Expression of Genes Involved in Regulation of Na+ Homeostasis" (569-P)
- "Effects of Long-Term Therapy (2-Year) with Muraglitazar, a Novel Dual PPAR A/Γ Agonist, on Diabetic Dyslipidemia in Patients with Type 2 Diabetes: A Double-Blind, Randomized, Parallel-Group Study" (967-P)
- "Improvement of Diabetic Dyslipidemia with Muraglitazar, a Novel Dual PPAR A/Γ Agonist, Plus Glyburide in Patients with Type 2 Diabetes Failing Sulfonylurea Monotherapy: A Randomized, Double-Blind, Placebo-Controlled Study" (968-P)
- "Attainment of A1C Goals with Muraglitazar, a Novel Dual PPAR A/Γ Agonist, in Combination with Metformin in Patients with Type 2 Diabetes: A Double-Blind, Randomized Comparison with Pioglitazone Plus Metformin" (2113-PO)
- "Lack of Pharmacokinetic Interaction between Glyburide and the Novel Dual PPAR A/Γ Agonist Muraglitazar" (2114-PO)
- "Lack of Drug Interaction between Metformin and Muraglitazar, a Novel Dual PPAR A/Γ Agonist under Investigation for the Treatment of Type 2 Diabetes" (2115-PO)
- "Statins Do Not Alter the Pharmacokinetics of Muraglitazar, a Novel Dual PPAR A/Γ Agonist under Investigation for the Treatment of Type 2 Diabetes" (2116-PO)

- Conjuchem
  - Conjuchem did not have a booth at ADA, but they did have three posters on DAC™:GLP-1 (CJC-1131):
  - "Effects of DAC-GLP:1 (CJC-1131) on Glycemic Control and Weight over 12 Weeks in Metformin-Treated Patients with Type 2 Diabetes" (10-OR).
  - "Lack of Immunogenicity Following Repeated Administration of CJC-1131, a Drug-Affinity Complex (DAC) GLP-1, in Monkeys" (2106-PO).

- "Absorption, Distribution and Elimination of CJC-1131 after Subcutaneous Administration" (2107-PO).
- Conjuchem also had a poster on the long-acting insulin analog that it is developing, "CJC-1525/CJC-1575: Long Lasting DAC™ Insulin Analogues for Basal Glycemic Control," which showed potentially intriguing pre-clinical data from rat studies (466-P).
- Given that Novo Nordisk's Levemir (insulin detemir) received FDA approval with a label for once or twice-daily administration on June 17, 2005, and Conjuchem's long-acting insulin analog has been shown in rats to outlast Lantus, it will be interesting to see in the next few years if Conjuchem's product can receive approval and whether it receives a label for once-daily dosing.

- Lilly
  - The Lilly booth focused heavily on Byetta and on Lilly's own insulin portfolio
  - In terms of its own products, Lilly was most promotional of insulin analogs:
  - Humalog Mix75/25, its 75% insulin lispro protamine suspension/25% insulin lispro premixed insulin analog formulation (formerly called Humalog Mix25) that competes with Novo Nordisk's NovoMix 70/30 aspart protamine/aspart product
  - Humalog, the first-in-class rapid-acting insulin analog that has been available in the US since 1996.
  - Lilly has embarked on a major rebranding campaign, with a slick new Humalog logo:

  - The rebranding is being supported by a new insulin injection pen, which we saw at Diabetes UK in April. It looks like a wood-grain Mont Blanc pen – rather large in size but very elegant. Whether it will be launched in the US, where insulin injection pens are less common than they are in Europe (only 12% market penetration, according to an Ypsomed press release regarding the FDA's approval of the Sanofi-Aventis Lantus pen Opti-Clik), is unclear at this stage. If it will be launched, AADE should offer an opportunity for further information.
  - Lilly gave away one of the most distinctive favors of ADA: a vibrating massager ballpoint pen. The pen is battery-powered so that when the top is depressed the whole pen vibrates. No kidding. Twisting the bottom half of the pen pushes out the ballpoint ink cartridge. We witnessed one bemused Novo Nordisk rep contemplating her options for obscuring the Lilly branding on the pen so that she could keep it.

    <u>Lilly/Alkermes HIIP posters</u>
  - "Dose Response and Dose Equivalency of Human Insulin Inhalation Powder (HIIP) Using the Lilly/Alkermes Inhaled Insulin System Compared to Subcutaneous (SC) Insulin Lispro" (360-OR)
  - "Safety and Efficacy of Preprandial Human Insulin Inhalation Powder (HIIP) Delivered by the Lilly/Alkermes Inhaled Insulin System Versus Injectable Insulin in Patients with Type 1 Diabetes (T1D)" (361-OR)
  - "Drivers of Treatment Preference for the Lilly/Alkermes Inhaled Insulin System in Patients (Pts) with Type 1 Diabetes (T1D)" (2055-PO)
  - "Patient Reported Outcomes (PROs) Using the Lilly/Alkermes Inhaled Insulin System Versus Injectable Insulin in Patients with Type 1 Diabetes (T1D)" (2056-PO)

    <u>Ruboxistaurin posters</u>
  - "Effect of Ruboxistaurin on Albuminuria and GFR in Persons with Type 2 Diabetes and Nephropathy" (223-OR)
  - "Selective Loss of Insulin's Effect on Akt and eNOS Activation in Renal Glomeruli in Insulin Resistant State – Role of Protein Kinase C Activation" (858-P)

- "PKC Activation in Endothelial Cells Paradoxically Promotes VEGF-Stimulated eNOS Ser1179 Phosphorylation Via AMPK While Inhibiting Insulin- and VEGF-Stimulated PI3K-Akt Signaling" (1992-P)

- Merck
  - Merck's booth did not highlight sitagliptin (MK-0431), the company's DPP-IV inhibitor. Merck did have eight abstracts about the compound, of which two were featured in oral abstract sessions and three were publish-only – a very good showing for a compound that is only in Phase 2
  - "Effect of Adding MK-0431 to On-Going Metformin Therapy in Type 2 Diabetic Patients Who Have Inadequate Glycemic Control on Metformin" (11-OR)
  - "Twelve-Week Efficacy and Tolerability of MK-0431, a Dipeptidyl Peptidase IV (DPP-IV) Inhibitor, in the Treatment of Type 2 Diabetes (T2D)" (41-OR)
  - "Single Doses of MK-0431, an Inhibitor of Dipeptidyl Peptidase-IV, Raise Active GLP-1 Levels without Causing Hypoglycemia in Healthy Subjects" (493-P)
  - "Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of MK-0431 over 28 Days in Middle-Aged, Obese Subjects" (497-P)
  - "Effect of MK-0431, a Dipeptidyl Peptidase IV (DPP-IV) Inhibitor, on Glycemic Control after 12 Weeks in Patients with Type 2 Diabetes" (541-P)
  - "Co-Administration of MK-0431 and Metformin in Patients with Type 2 Diabetes Does Not Alter the Pharmacokinetics of MK-0431 or Metformin" (2099-PO)
  - "Multiple Dose Administration of MK-0431, a Dipeptidyl Peptidase IV (DPP-IV) Inhibitor, in Healthy Male Subjects" (2099-PO)
  - "Lack of a Clinically Meaningful Effect on Age, Gender or Obesity on the Pharmacokinetics of the DPP-IV Inhibitor MK-0431" (2101-PO)
- Metabolex
  - We were privileged to have an interview with Dr. Harold van Wart, President and CEO of Metabolex, regarding metaglidasen (MBX-102), Metabolex's novel non-TZD insulin sensitizer. Some highlights concerning the compound itself and Metabolex's strategy to advance it:
  - Metaglidasen is a single isomer of halofenate, a lipid-lowering agent that was originally discovered by Merck in the 1970s but never commercialized because halofenate was associated with gastrointestinal side effects, including ulcers. Because metaglidasen is a single isomer of the compound, those same safety concerns may not apply to metaglidsen; further studies will tell.
  - It was discovered in Merck's original Phase 3 trial that 50 type 2 diabetic patients who had been accidentally enrolled saw lower glucose levels as well as lower lipids (*We like it when stuff like this happens – ed.*)
  - Matabolex notes reason that metaglidisen does not appear to cause weight gain or edema is that it does not act on the same genes that Actos or Avandia act on to cause these side effects (*We will be learning more about this – ed.*)
  - In a recent Phase 2 trial, metaglidisen showed comparable glucose and lipid control to Actos and Avandia in high-risk patients who were already taking insulin but still out of control
  - No other oral antihyperglycemic agents were used in the study. Some patients were previously taking sulfonylureas, metformin, or alpha glucosidase inhibitors but these were discontinued before the study began. Many of the patients were on statins
  - HDL to LDL ratio remained about the same, but the study was not powered for this – the Phase 3 trial that is planned will be powered for this, though
  - The high-risk patient population was specially selected because it would be the true test of whether metaglidisen were truly different from the established TZDs in terms of congestive heart failure (CHF) risk. Similar studies using Actos and Avandia were published in previous years so this trial was not a new design

- Study baseline: n = 217, average A1C of 9.1% (range 7.5–11.5%), avg. total daily dose of 50 units insulin/day. Average age 53-54 years, diabetes duration 14 years, no data available re duration of insulin therapy (no data available regarding exact insulin regimens: insulin types, injection frequency, etc.)
- Patients randomized to 200 mg metaglidasen, 400 mg metaglidasen, or placebo – see ADA abstract 44-OR for results
- Right now, plans are in progress to do Phase 3 trials in the next year but this depends on the FDA meeting that is scheduled to happen in 4Q05
- There is a second study ongoing to see whether a 600 mg dose of metaglidasen is even more effective than 200 or 400 mg. There were no dose-limiting side effects observed with the 200 or 400 mg doses, so 600 mg is being tried
- In terms of international prospect, Dr. Van Wart said that he would like for metaglidasen to become available worldwide and Metabolex wants international partnerships to make that happen.
- The EMEA warns against combining insulin and a TZD because of the risk of CHF, so in Europe metaglidasen will probably be positioned differently from how it is being described in the US at present.

- Novartis
  - We were fortunate to have an interview with Dr. Tom Hughes, a Novartis scientist who has been very involved in the development of vildagliptin, Novartis's DPP-IV inhibitor. High points indicative of Novartis's strategy with this compound:
  - By working only to allow endogenous levels of GLP-1 to work better, DPP-IV inhibition would prevent GLP-1 concentrations from becoming great enough to cause nausea (this seemed to be a reference to nausea as a Byetta side effect, which was interesting in and of itself – some who are using Byetta actually say that people seem to think they are nauseous when they are just not hungry
  - Is there enough endogenous GLP-1 available to have a beneficial effect if DPP-IV is inhibited in a GLP-1 deficient type 2 diabetes patient? Dr. Hughes's answer to this was to say that one couldn't distinguish between the effects of injected GLP-1 and the effects of DPP-IV inhibition.
  - Do DPP-IV inhibitors really work only by inhibiting GLP-1? Dr. Hughes said that this has been demonstrated by the use of DPP-IV knockout mice: vildagliptin has no effect if DPP-IV is knocked out, and if you knock out GLP-1 and GIP, vildagliptin doesn't do anything either.
  - In response to concerns regarding whether any negative consequences might arise from inhibiting DPP-IV because of crosstalk being interrupted, Dr. Hughes explained that, while research is on-going, it seems as though there is redundancy within the body's enzymes so that anything else for which DPP-IV might be useful can be accomplished by another enzyme, and that that no essential processes seem to be interrupted by the inhibition of DPP-IV.
  - Results of a "very large, robust" Phase 3 monotherapy and combination therapy clinical trial that should prove vildagliptin's safety are expected to be out in 2006. An animal safety program is ongoing as well.
  - While we feel that the advantage of Byetta in terms of weight loss places it ahead of DPP-IV inhibitors, which are apparently weight-neutral, we wonder if combination therapy involving Acomplia and vildagliptin might be a significant possibility. We will watch for more data on this.

    <u>Vildagliptin posters</u>
  - "Head-to-Head Comparison of the DPP-4 Inhibitor Vildagliptin with Exendin-4 in a Model of Pancreatic Beta Cell Injury" (267-OR)
  - "The DPP-4 Inhibitor Vildagliptin Increases Pancreatic Beta Cell Neogenesis and Decreases Apoptosis" (572-P)

- "Beta-Cell Expression of a Dominant-Negative Hepatocyte Nuclear Factor (HNF)-1alpha Compromises the Ability of DPP-4 Inhibition to Elicit a Long-Term Augmentation of Insulin Secretion in Mice" (1533-P)
- "Improved Meal-Related Beta Cell Function and Dynamic Insulin Sensitivity by the DPP-4 Inhibitor Vildagliptin in Metformin-Treated Patients with Type 2 Diabetes over 1 Year" (2121-PO)
- "Combination of the DPP-4 Inhibitor Vildagliptin (LAF237) with Pioglitazone Is Safe and Well Tolerated with No Pharmacokinetic Interaction" (2192-PO)
  This study reported no data on weight gain, which we imagine was probably considerable as it usually is with efficacious TZD therapy. If weight loss had been observed, we can't imagine Novartis not reporting it. We would love to know, if the combination of a DPP-IV inhibitor with a TZD showed a little more or a little less weight gain than is often observed in TZD initiation even if the difference was not statistically significant.

- Novo Nordisk
  - As it was at last year's ADA, Novo Nordisk's booth was a two-story wooden structure with glass walls this year. Very sleek! On one corner, a chef prepared healthy snacks and a diabetes educator presented strategies for healthy eating, including portion control and calorie-saving food substitution ideas (using Laughing Cow instead of cream cheese, buying small bagels rather than big ones, etc.). This was interesting as it didn't tie directly to products, but did garner more booth traffic.
  - Although Levemir wasn't yet approved, there was lots of interesting analog mix data out and the booth appeared quite packed
    Young Voices book
    In a compelling combination of a public service project and durable promotional literature, Novo has published with John Wiley & Sons an attractive hardcover book called *Young Voices: life with diabetes*, written by Hala Khalaf. The book was formally launched in the US at ADA. The book profiles thirteen individuals ranging in age from young childhood to middle age that were all diagnosed with diabetes in their youth. Three of the patients have type 2 diabetes. The book highlights differences among national and individual attitudes to and strategies for diabetes management. *Young Voices* is dedicated to the memory of one child profiled, a 5 year-old Tanzanian girl who died of complications of type 1 as the book was in production. Proceeds from the sale of the book on Amazon will be donated to Novo's Tanzanian diabetes clinics.
  - With over 200 employees registered to attend the meeting, Novo may have been the best represented company at ADA. Displays at the booth focused on the 70/30 insulin analog FlexPen and NovoLog, but as noted not on Levemir because Levemir was not approved until Friday, June 17. Even if Levemir had been approved, we believe they would have still promoted 70/30 widely – and we believe they will continue to do so as they promote their full set of therapies.. Novo's ADA poster 458-P, "Similar Pharmacodynamic and Pharmacokinetic Dose-Response Relationship of Insulin Detemir and NPH Insulin in African Americans, Hispanics or Latinos and Caucasians," provided the ethnic data that we are given to understand cleared the final hurdle for Levemir's approval. This was great to see.
  - While most hallway chatter centered around Byetta because it has been approved and clinicians and researchers are now debating how it will be used in clinical practice (some are waxing quite lyrical about potential off-label uses), Novo Nordisk's Liraglutide got quite a lot of exposure in the posters, with one of six accepted abstracts featured in an oral abstract session and only one in the "publish-only" category:
  - "Liraglutide, a Long-Acting GLP-1 Analog, Restores Pancreatic Beta-Cell Mass and Corrects Hyperglycemia after Diabetes Onset in NOD Mice: Gastrin Potentiates Liraglutide's Effects" (232-OR)

- "No Difference in Pharmacokinetic Profile of Liraglutide When Administered as a Single Dose to Young and Elderly Healthy Subjects" (460-P)
- "Liraglutide Reverses Diabetes in Psammomys obesus, a Model of Type 2 Diabetes" (500-P)
- "The TGF-beta Pathway Is Involved in the Regulation of Gene Expression Induced by the Long-Acting GLP-1 Analogue Liraglutide in Human Pancreatic Islets" (1115-P)
- "The Long-Acting GLP-1 Analog, Liraglutide, Increases Beta Cell Numbers during Early Human Development" (1636-P)
  This abstract is key in our view because it used fetal pancreatic cells obtained from voluntarily terminated pregnancies to show the effects of Liraglutide on beta cell proliferation and/or inhibition of apoptosis in the developing human pancreas. Results showed more beta cells in the tissue treated with Liraglutide than in the control tissue, but the results were not specific enough to indicate whether enhanced proliferation or reduced apoptosis was responsible for the increase in beta cells. While it can be thorny ethical ground to do experiments such as these and this sort of basic research might well not receive funding within the US (the present study was conducted in the UK), this study may have implications for the design of future research projects involving Byetta.
- "Simulating Long-Term Outcomes of Liraglutide+Metformin Versus Metformin and Metformin+Glimepiride in Type 2 Diabetes Patients with Inadequate Glycaemic Control" (2545-PO)
  This study using computer models produced preliminary results that might be confirmed through in vivo studies designed similarly to the 3 Amigo studies conducted by Amylin
- Novo also showed a poster ("Biphasic Insulin Aspart Thrice Daily Is as Efficacious as Traditional Basal Bolus Regimen with Four Daily Injections in Subjects with Type 2 Diabetes" – 496-P) discussing its new biphasic insulin formulations: 50/50 and 30/70 (the latter reverses the ratio of intermediate- to rapid-acting insulin that their 70/30 features). The principle of traditional 70/30 is to provide a small amount of short- or rapid-acting insulin and most of the dose in the form of intermediate- acting insulin. If dosing is not matched to a patient's diet and activity pattern, this approach can lead to postprandial hyperglycemia followed by hypoglycemia several hours after a meal. Reversing the ratio to provide a lot of rapid-acting insulin and a little intermediate-acting insulin may improve postprandial and interprandial glucose levels in patients for whom a basal/bolus regimen involving two different insulins (one basal, one bolus) is not entirely appropriate.

- Pfizer
  - Pfizer's showcasing of Lyrica (pregabalin) at the ADA might be characterized as anticlimactic: the drug is still being formally classified according to the marketing website http://www.lyrica.com, so the drug was not launched at the ADA despite the expense that it appeared that Pfizer had undertaken to promote it: a large booth decorated with signs exclaiming "coming soon!" may not have been Pfizer's plan when they booked the booth.
    <u>Lyrica posters</u>
  - "Pregabalin Reduces the Sleep Interference Associated with Painful Diabetic Peripheral Neuropathy" (539-P)
  - "Efficacy, Safety, and Tolerability of Pregabalin Treatment for Diabetic Peripheral Neuropathy: Findings from 6 Randomized Controlled Trials" (551-P)
  - "Pregabalin Provides Significant Improvement in Overall Clinical Status and Health-Related Quality of Life in Patients with Diabetic Peripheral Neuropathy: Findings from 6 Randomized Controlled Trials" (563-P)
  - "Long-Term Treatment of Painful DPN and PHN with Pregabalin in Treatment-Refractory Patients" (564-P)
  - "Pregabalin Significantly Reduces the Pain Associated with Diabetic Peripheral Neuropathy by Day One of Treatment" (602-P)
  - Exubera posters (in collaboration with Sanofi-Aventis)

- "Exubera Is Well Tolerated and Achieves Tight Glycemic Control in Patients with Type 1 Diabetes" (355-OR)
- "Long-Term Use of Exubera in Type 2 Diabetes: Observations on Glycemic Control, Pulmonary Function and Antibody Formation" (356-OR)
- "Validation of Radiolabeled Insulin Powder for Exubera Studies" (433-P)
- "Inhalation of Insulin (Exubera) Augments the Efficiency of Muscle Glucose Uptake In Vivo" (435-P)
- "Immunologic Response to Exubera in Patients with Type 1 Diabetes Is Not Associated with Functional Evidence of Airway Sensitization" (437-P)

- Sanofi-Aventis
  - At the Sanofi-Aventis booth, which was branded more as a Lantus booth, the new OptiClik injection pen received much focus from representatives. When Lantus was first launched, the injection pen was not acceptable to most patients, who tended to find it difficult to handle and uncomfortable to use. Sanofi-Aventis took the pen device back into development and recently launched OptiClik in Europe. OptiClik made its grand entrance into the US market at the AACE meeting in May.
  - The pen features a digital display of the number of units dialed up. This digital display should increase patients' accuracy in dosing. The pen offers 1-unit dosage adjustment increments.
  - We have been given to understand for much of the past year, since the 2Q04 approval of Apidra (glulisine), Sanofi-Aventis's rapid-acting insulin analog that has still not been formally launched, that approval of the new Lantus pen would basically signal the impending launch of Apidra. Hallway chatter at ADA indicated that some physicians have already received samples of Apidra but pharmacies are unlikely to have it in stock until early 2006.
  - We remain unclear regarding what (if any) alterations to the OptiClik pen technology may be effected before the Apidra launch. Thus far, no Sanofi-Aventis rep has been able to tell us if the Apidra pen will allow half-unit (or smaller) dosage adjustment increments. Conceivably, an insulin injection pen that has a digital display could be engineered to allow for doses by the half-unit or even smaller increments. A rapid-acting insulin analog injection pen that could offer, for instance, 0.2 unit dosage increments would be a real hit among intensively managing multiple-daily injectors and among highly insulin-sensitive patients, especially children. We will keep watching this topic for further developments.
  - According to Dr. Tim Heise's ADA Symposium presentation "New Insulins: Are All of the Rapid-Acting Analogs," one key difference between lispro and aspart compared to glulisine is that lispro and aspart preparations contain zinc, but glulisine has polysorbate 20 because it will behave pharmacokinetically like human regular insulin if it is mixed with zinc
  - The implication of this finding is that, when it is launched in the US, glulisine (brand name Apidra) may come with the warning that it is not to be mixed in the same syringe with an intermediate-acting insulin. Glargine (Lantus) is not supposed to be mixed with other insulins either. Whether patients will prefer to use Apidra and Lantus and take more shots to achieve glycemic control or whether they would rather take fewer shots and use other insulins like NovoLog and Levemir, which we believe will be mixable, time and IMS Health data will show.

- ADA session of note
  - "Oral Abstracts: Insulin Inhalers and Patches"

    359-OR: AeRx is a breath-activated, liquid formulation of inhaled insulin. AeRx study results presented by Astrid Petersen indicated a 142-minute duration of action for AeRx, 202 minutes for subcutaneous human R, and 136 minutes for subcutaneous insulin aspart (NovoLog). The results of the study also indicated a similar time to onset of action compared to insulin aspart. The 14-minute difference in duration of action was not statistically significant.

These results fall into line with what we have seen from MannKind's Technosphere inhaled insulin product, perhaps suggesting a class effect with inhaled insulin of a comparable onset of action vs. a rapid-acting analog but a duration of action more like human regular.

The AeRx study was conducted in type 1 patients with an average age of 34 years and a BMI of 24.5, which may not be typical of the population for whom inhaled insulin represents an attractive therapy option – namely, overweight, insulin resistant type 2s whose control does not need to be perfect, but for whom slightly better control could make a big difference in outcomes.

361-OR: Dr. Satish Garg of the Barbara Davis Center and the University of Colorado presented some interesting data regarding the safety and efficacy of preprandial Lily/Alkermes inhaled insulin compared to subcutaneous human regular or insulin lispro.

We find it interesting that Lilly is comparing its inhaled product to its currently available short- and rapid-acting insulin products: a statement of great confidence in the inhaled technology as we see it.

The primary endpoint of the study was to determine non-inferiority of inhaled insulin compared to subcutaneous R and lispro by an absolute change in A1C of no more than 0.3%. The secondary endpoints were to collect seven-point SMBG glucose profiles and to assess safety of the inhaled product.

The patients in the study were all type 1s taking insulin glargine (Lantus) for basal insulin coverage and used either insulin lispro or human Regular for mealtime insulin. Their average age was 39 and their BMI was 28.1. Before the study, 70% used insulin lispro at meals and 30% used human regular insulin. The average A1C of the group was 8.1%. The primary endpoint of non-inferiority in terms of A1C change was achieved.

The seven-point blood glucose profile data was, however, more interesting: in the inhaled insulin group, fasting blood glucose values were significantly lower than the fasting blood glucose levels of the subcutaneous insulin takers despite identical levels of basal insulin glargine. This trend has also been observed in trials of Exubera; perhaps there is a class effect in evidence?

- As well, the inhaled insulin group showed a much greater risk for nocturnal hypoglycemia compared to the subcutaneous insulin users.
- Combined, the lower fasting glucose levels and increased risk for nocturnal hypoglycemia go a long way to suggest to us that the true duration of a dose of a dose of inhaled insulin might be much longer than the time indicated by controlled laboratory testing.
- Dr. Garg disclosed that the postprandial glucose values of the inhaled insulin users were higher than those of the subcutaneous insulin takers.

  Thus, higher postprandial blood glucose levels and lower nighttime blood glucose levels averaged to maintain near-identical A1C results despite what could be considered a deterioration in the quality of their control.

CUTTING THE FAT AT THE ADA: FOCUS ON OBESITY

Obesity held a huge place at this year's ADA, with sessions on the topic taking place every day in every time slot, l-i-t-e-r-a-l-l-y. Below are selected topics related to obesity that we found interesting in the many sessions we attended. Topics cover about one zillion aspects of the epidemic, including the politics of obesity, its costs and cost-effectiveness of treatment, pharmaceutical treatments of obesity, environmental factors that contribute to the epidemic, and the social consequences of obesity. The ADA session on gastric bypass surgery was so remarkable that we couldn't help but give it its own separate article, which follows this one. (This is in keeping with our response to ADA Postgrad in January, where gastric surgery also represented among the very best sessions.)

Plenary Lecture: "The Politics of Obesity"

Is the food industry to blame for the growing obesity epidemic? In large part, yes (exclamation point) according to Marion Nestle, obesity expert and Paulette Goddard (read: bigwig) Professor of Nutrition, Food Studies, and Public Health at New York University[5], author of *Food Politics* and *Safe Food*, thought-leader in nutrition, and the former managing editor of the 1988 Surgeon General's Report on Nutrition and Health. Dr. Nestle began her talk on the politics of obesity by isolating the determinants of dietary choice:

- economic status
- social influences such as education, age, peers, gender, culture, and family
- the food system

The "food system" includes production and marketing, and deserves much more focus (and blame) than it currently receives as the culprit of poor dietary choices, according to Dr. Nestle. She characterized the food system as "big business" (~$1 trillion/year), cheap, consumed outside of the home about half the time, and overabundant. On that last note, Dr. Nestle reported that the U.S. food supply produces 3,900 kcal/day for each person in the United States each day, which is almost twice the caloric intake that the average person *needs* to maintain current weight. Also, this number is up 600 kcal/day since 1980, and Nestle feels it's no coincidence that people are eating more now than they were in 1980.

Food and beverage companies spend $36 billion per year on marketing in the US – more than half the US government's annual spending on education. Not only does the food industry advertise heavily, but much of its advertising is directed toward children, who are too young to exercise informed personal responsibility. Dr. Nestle underscored three goals that food and beverage companies have in mind when marketing to children – perhaps a bit reductive, but we can her points:

- instill brand loyalty at an early age
- work the "pester factor"—get children to nag their parents for certain food and beverage products
- promote the notion that children are supposed to eat "kid foods" instead of adult foods such as foods in odd shapes and colors. Nestle pointed out the complicity of healthcare professionals in this matter. For example, Cookie Crisp Cereal and Cocoa Puffs breakfast cereals are endorsed by the American Heart Association.

How can the government help solve this dilemma? Dr. Nestle recommends that the government regulate television advertising aimed at children and increase subsidies for fruits and vegetables. Also, there is a need for more supermarkets and healthy food options in low-income areas. (*We have noted that organic food is cheaper in San Francisco's Pacific Heights than is in East Oakland – ed.*)

ADA Symposium: "Return on Investment: Is Treatment of Obesity Cost Effective?"

The three speakers of this session each presented a unique angle in assessing reimbursement for obesity treatments and the cost-effectiveness of such treatments. Anne Daly, former ADA President of Health Care and Education, began the session with an overview of current health care costs of obesity.

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[5] According to her website www.foodpolitics.com, Nestle's degrees include a Ph.D. in molecular biology and an M.P.H. in public health nutrition, both from the University of California, Berkeley. Nestle's research, her bio notes, focuses on analysis of the scientific, social, cultural, and economic factors that influence the development, implementation, and acceptance of federal dietary guidance policies. As many of you know, Nestle is the author of *Food Politics: How the Food Industry Influences Nutrition and Health* (University of California Press, 2002) and *Safe Food: Bacteria, Biotechnology, and Bioterrorism* (University of California Press, 2003), and is co-editor of *Taking Sides: Clashing Views on Controversial Issues in Food and Nutrition* (McGraw-Hill/Dushkin, 2004).

According to Daly, obesity racks up direct costs of $63 to $98 billion each year, including hospital and nursing home services, visits to health care professionals, medications, and personal health care. Daly reported that obesity creates another $40 billion in indirect costs each year. Health care costs for obese patients are 37% higher than for patients of healthy weight and 60% higher for morbidly obese patients. Morbid obesity (BMI >40) is rising twice as fast as obesity (BMI >30). With these increased costs and the rising prevalence of obesity, we can expect obesity to take an increasingly large toll on the health care system.

Daly also spoke in detail on reimbursement for obesity treatments. She said that at best, most coverage is limited—"not mandated or encouraged" and that the ICD-9 code for obesity is a "red flag for denial—it never gets reimbursement." Instead, physicians must mark other pertinent codes, such as cardiovascular disease, dyslipidemia, diabetes, or metabolic syndrome. At the heart of the matter is the question of whether obesity is a disease. The World Health Organization, the National Institutes of Health, the Centers for Disease Control and Prevention, the American Dietetic Association, and the Internal Revenue Service all consider obesity to be a disease. The IRS recognized obesity as a disease in July 2002 and has since allowed payments for medically valid obesity treatments to be claimed as tax deductions. On the other hand, proponents of the classification of obesity as a lifestyle choice reject its classification as a disease.

Daly discussed health insurance coverage (or lack thereof) for bariatric surgery. The costs of this procedure vary widely: the average cost nationwide is $25,000 per surgery, while the statewide average cost in California is $64,000. Bariatric surgery coverage is excluded in most basic healthcare coverage packages, and some companies that cover the procedure require that the beneficiary participate in a physician-supervised weight-loss program for at least six to twelve months without success before surgery in order to receive coverage. Some insurers (CIGNA, Blue Cross/Blue Shield of Florida and BC/BS of Alabama) began covering bariatric surgery but then dropped it, most likely because demand for surgery surged after they initiated coverage. Other states, including Connecticut, Georgia, and Louisiana, are proposing mandates for coverage.

In her remarks, Anne Daly said that obesity and its complications will "break the bank unless prevention and treatment become more effective and accessible." She noted that reimbursement is a key incentive to provide effective treatment, since physicians will hesitate to treat obesity if they know they won't be reimbursed for it. Risk reduction vs. high up-front investment remains a hard sell among insurance providers, but Daly stressed that paying for cost-effective obesity treatment is a necessary step to improve health and reduce health care costs.

Anne Wolf from the University of Virginia School of Medicine followed Daly. Wolf outlined six criteria that make a treatment justified, and explained how these criteria are applied to the treatment of obesity:

- *What is the magnitude of the problem to be addressed by treatment?* It doesn't get much bigger than the obesity epidemic.
- *Efficacy: Can the intervention work?* According to Wolf, lifestyle intervention to treat obesity has 6 – 8% efficacy, medication (Xenical and Meridia) has 7–10% efficacy, and bariatric surgery has 20–35% efficacy.
- *Effectiveness: Does the intervention work?* For lifestyle intervention and medication, it depends on the patient. For bariatric surgery, the answer is yes.
- *What are the benefits and harms of the intervention?* Lifestyle intervention, medication, and bariatric surgery all decrease morbidity and prevent or manage diabetes. Lifestyle intervention causes minimal harm; medication poses risks of moderate harm, and bariatric surgery can cause moderate to high levels of harm.
- *Cost analysis: What does the intervention cost?* Annual estimated costs: Weight Watchers, $560; diet and exercise with a registered dietitian, $450-$1,200; physician-supervised weight loss program,

$2,000–$3,500; pharmacotherapy (phentermine, $245- $735; sibutramine, $1090-$1434; orlistat, $1300); bariatric surgery, $20,000–$25,000+ (more in CA!)

- *Cost effectiveness: How do benefits compare with the costs?* It is not at all difficult to make the argument for surgery:
  - Lifestyle intervention – results from the Diabetes Prevention Program indicate that metformin costs $31,000 per quality-adjusted life year (QALY), and the lifestyle intervention QALY measure was $1,100. Generally, a QALY measure under $50,000 is considered cost-effective. Anna Wolf interpreted these data to mean that metformin treatment is cost effective, and lifestyle intervention is *completely* cost effective.
  - Pharmacotherapy: medication to treat obesity in people with type 2 diabetes decreases their need for diabetes medications. In a study of Xenical + diet change vs. placebo + diet change, obese subjects in the Xenical group lost an average of 6.2% body weight, while subjects in the placebo group lost 4.3%. 43.2% of sulfonylurea use was reduced in the Xenical group, vs. 28.9% in the placebo group. Sulfonylurea use was discontinued in 11.7% of patients in the Xenical group, vs. 0% in the placebo group. Wolf admitted that sulfonylureas are not all that pricey, but her point was that treating weight loss may reduce healthcare costs by decreasing other prescriptions. The QALY measure for treating obese patients with type 2 diabetes is $19,986.
  - Bariatric surgery: Wolf gave bariatric surgery a mixed review. On the one hand, the Swedish Obese Subjects study (SOS), which ran over a six-year period, found that the control group had lower annual healthcare costs than the surgery group, even excluding the cost of surgery. On the other hand, researchers in Canada found that after about 3.5 years, the healthcare costs of the bariatric surgery group were less than the costs of the control group, including the cost of surgery. However, as Wolf pointed out, Canada's surgical costs are much lower than those in the United States. Also, obesity decreases productivity in the workplace. In the Canadian study, productivity was higher for the surgery group than for the control group two years after surgery.

The final speaker of this session was Scott MacFarland from HealthCare Dimensions, Inc. in Tempe, Arizona. MacFarland spoke from the payor's perspective. He stated that in the US, employers bear 58% of the financial burden of healthcare; Medicare and Medicaid account for 12% and 11%, respectively; and individuals pay for 5%. The rest of the American population is uninsured. Employers, therefore, have a very important stake in determining which procedures are covered by healthcare insurance. MacFarland noted that consumer-driven health plans, which made up 40% of healthcare insurance plans in 2003, are expected to experience significant growth in the future. Under these plans, consumers can elect to use a certain portion of their group health plan benefits toward whatever treatments they choose. Businesses have a lower stake in making health care decisions for employees under these plans. MacFarland also addressed the risk vs. long-term investment issue mentioned by Anne Daly. He pointed out that people in the US usually only stay with an insurance carrier or third-party payor for an average of three years. As a result, companies usually do not want to make long-term health investments. (Close Concerns notes that, on average, obese patients and patients with diabetes may stay with plans longer because getting healthcare insurance at all is such a challenge if one has a pre-existing condition.)

Pharmaceutical Treatments for Obesity

The most talked-about drug for obesity without a doubt is Acomplia (rimonabant), but the data at this meeting really focused more of patients with diabetes, not just obese patients. We view a diabetes label as a challenge for Acomplia.

During a well-attended symposium on the "Lifelong Challenges of Obesity" (sponsored by Abbott), Dr. Donna Ryan from Louisiana State University gave overviews of Meridia and Xenical. But first, she emphasized that "lifestyle interventions are the foundation" of any weight loss attempt, and thus Meridia

and Xenical should be prescribed with a sensible diet and exercise plan. Meridia was positioned as having a "favorable" side-effect profile, and the weight loss in patients taking Meridia improves their lipid profile and body composition, and is associated with a mean blood pressure decrease, despite the hype about Meridia raising blood pressure levels. There are many patient anecdotes about very tough side effects. According to the STORM trial, over 75% of patients achieve more than 5% weight loss when given Meridia with behavioral intervention over two years. Three other studies found that ~66% of patients achieved at least 5% weight loss while taking the drug. While Meridia has a dose-related effect on blood pressure, studies show that a blood pressure decrease occurs in patients who lose more than 5% of their weight while taking Meridia (the majority of patients). Dr. Ryan appeared confident that every physician can manage Meridia's effects on blood pressure. (Personally we thought one of the most interesting aspects of this symposium was reports of how people feel about the word *obesity*. Unsurprisingly, patients hate it and they're not excited about clincial use of the term.)

Shifting to Xenical: Xenical was touted as the number-one prescription weight loss medication in the US. This news is actually not all that remarkable, as today obesity drugs sell less than $1 billion worldwide, while drugs for cardiovascular disease sell $60 billion. (Statins alone are worth a cool $26 billion per year.) And diabetes drugs appear to generate upwards of $15 billion. The <$1 billion that obesity drugs are worth is *nothing*! However, Xenical is likely to be available over-the-counter in 2006, and it will be interesting to see how that goes since Roche quietly pulled all marketing support from Xenical some time ago. Tolerability has been a major issue with Xenical to date. The drug has been known to cause GI side-effects and steatorrhea (we won't go into the details; suffice it to say that it is apparently as unpleasant as it sounds). Because the drug interferes with the absorption of nutrients, vitamin supplementation is required for long-term use. Weight loss on Xenical was positioned as capable of improving glycemic control, lipids, waist circumference, and blood pressure – but tolerability and compliance are both low. Dr. Ryan mentioned that patients taking Xenical often learn how to avoid its GI side effects by altering their diet and drug regimen, such as skipping a dose when expecting to eat a high-fat meal and when taking the drug, restricting their fat intake. A large (n=539), randomized double-blind trial on the safety and efficacy of Xenical as treatment for obese adolescents was published in *JAMA* on June 15 this year. Based on their results, the authors of the study concluded that Xenical, in conjunction with diet, exercise, and behavioral modification, significantly improves weight management in obese adolescents. Encouraged by this study, European regulators recently extended Xenical's approval to cover use in adolescents. The original US label allowed for Xenical use in both adults and adolescents.

In addition to these obesity drugs, there has been much discussion of other medical technologies to treat obesity. For now, God knows, we need them –today, one third of all Americans are obese and another one-third of the population is overweight. The obesity epidemic is not limited to the United States; the prevalence of obesity has been growing in Europe and Asia as well, in developed and developing countries alike. It is oft-said that obesity is now a bigger global problem than starvation. How to treat (or, how not to)? It is estimated that ninety percent of people 'fail' diet and exercise prescriptions; despite this, only 4% of obese patients are treated with drug therapy – compared, for example, to 66% of hypertension patients who are treated with drug therapy and 79% of patients with diabetes. Whereas the global market for obesity drugs remains well under $1 billion, the size of the drug markets for diabetes and cardiovascular disease are upwards of $15 billion and $60 billion, respectively. There have been myriad problems with the safety of obesity drugs historically and even today, with just two left on the market, the side effect profiles are extremely problematic, resulting in big compliance problems in small markets. While we wait for better drugs and devices, a range of treatments for the morbidly obese to the slightly-high-BMI (say it, it rhymes) are of interest to us as multiple segments emerge. Whereas drugs to date haven't been especially effective in prompting weight loss over 5–10% of total weight, this is more than enough loss for some – if they can only maintain it! We'll see if Acomplia helps – we believe it should and that Sanofi-Aventis is doing smart things by focusing on the cardiovascular front - improving lipid profile – as much as sheer weight loss (to say nothing of smoking - we had assumed that would be the

first indication, but a recent press release pointed out the company "also" had smoking programs - interesting nuances on this at ADA).

In addition to drugs, procedures are clearly having a major impact on how we address weight as a country – and globe – and this will become more the case as more minimally invasive devices emerge (check out what happened on this front in orthopedics!). Just a few days ago, Medtronic announced its purchase of Transneuronix, Inc., a private medical device company that produces an implantable gastric stimulator (IGS) to treat obesity. The device, called Transcend, is often compared to a pacemaker and sends small electrical pulses to the stomach that create a sensation of fullness. The first implant took place in 1995; since then, more than 700 patients have been implanted with Transcend, and it is hoped that the device will continue to demonstrate excess weight reductions and a favorable safety profile. The device has been commercially available in Europe for more than three years, and it recently received approval for marketing in Canada – in the US, we'd look for approval if all goes well, around 2007. Enrollment in pivotals is complete – one-year data is needed for FDA submission and two years of data will be needed to gain approval, we would assume, similar to Lap-Band. Medtronic paid $260 million upfront – if that sounds cheap (which it did to us initially, even though we expect majority shareholders [read: management] are mightily pleased), potential earn-outs sound significant. Note that Medtronic's acquisition of Transneuronix comes soon after its announcement during its last earnings call of its new business unit called Medtronic Obesity Management. As noted in our last *DCU* (#48) we were intrigued but didn't expect the company to act this swiftly – hooray!

We couldn't find out very much about investors in Transneuronix (excepting Medtronic and management), and so we looked for further information on companies in the area of gastric pacing stimulation devices, notably Leptos, EnteroMedics and IntraPace, in order to further our thinking in this area. Karen Boezi, managing partner and co-founder of Thomas, McNerney & Partners and board member of Leptos, noted when we spoke with her about this deal that the obesity segment seemed to be shaking out a lot like cardiology. That is, in cardiology, there are segments of patients, with some best served by surgery, others by devices, others by combinations. The enormous number of pathways suggests that there won't be a, as is one, winner – depending on efficacy, there could be many (many, many) and the potential probably isn't as much about stealing share as much as growing the pie. Indeed, awareness is growing, largely thanks to CMS' decision to term obesity a disease – that, in turn, is spawning more investment in trials. The more that evidence can back up efficacy and safety, the faster the markets will grow – for sure, demand is huge.

Right now, the pie isn't *that* big for obesity drugs because there aren't any good ones and in terms of what it could be (especially given current slope), it isn't huge for surgery either, although it's growing, big-time. There has been an eightfold increase in the number of annual bariatric surgeries performed during the last decade, for example, and an estimated 140,000-plus gastric bypass surgeries alone last year in the US, plus another close to 20,000 Lap-Band (by Inamed) procedures. Just wait 'til gastric pacing becomes available, likely first in 2007 via the IGS. Needless to say, we expect to see (further) significant increases in surgeries, both minimally and maximally invasive, going forward. In the meantime, spending just on books for diet and exercise is the tens of millions annually – look at shortly for a new tome by Dr. Harriett Mogul, who is one of the sagest clinical minds around in our book.

Environmental and Social Influences on Behavior

Some say that obese people should be able to fix their problem themselves. Others ask, *How can obese people let themselves get like that anyway?* In response, we call attention to the environmental and social factors that affect eating behaviors and physical activity. Tiffany L. Gary, Ph.D., from the Johns Hopkins School of Public Health, touched on several of these factors, noting that social inequality,

differences in education levels and employment opportunities, as well as neighborhood characteristics and racial segregation, all strongly influence eating habits and levels of exercise. Obese people tend to have lower levels of education and employment, but whether that is a cause, effect, or both in a vicious cycle, is unclear. In neighborhoods, the accessibility of recreational resources such as parks and playgrounds affects sport and leisure time physical activities. Transportation options, sidewalks, and bike lanes also affect levels of physical activity. Crime is an important determinant as well, with the crime rate being a significant correlate to physical activity in African American women living in urban areas. Interestingly, crime was not a correlate to physical activity for white, Latina, or Native American women. Urban sprawl also has negative effects on BMI and chronic health problems. In their study published in *Public Health* in 2004, Sturm and Cohen concluded that "an increase in sprawl from one standard deviation less to one standard deviation more than average implies 96 more chronic medical problems per 1000 residents, which is approximately similar to an aging of the population of four years." The final factor that Dr. Gary spoke on was the distribution of supermarkets and restaurants. As earlier noted, there is a higher availability of supermarkets and healthy food options in wealthy neighborhoods. According to Dr. Gary, African Americans' fruit and vegetable intake increased by 32% for each additional supermarket in the census track, while fruit and vegetable intake only increased by 11% for the white population. She mentioned that there are many more fast food restaurants in areas of Los Angeles with a high African American population than in areas where most of the population is white (25.6% vs. 11.2%). Some neighborhoods have fast food restaurants galore but not a single supermarket or sit-down restaurant, which inevitably influences eating behavior.

Social Consequences of Obesity

Despite the multiplicity of factors that affect physical activity and eating habits, there remain striking prejudices against obese people. Dr. Thomas Wadden, the current President-Elect of the North American Association for the Study of Obesity (NAASO) and Professor of Psychology at the University of Pennsylvania School of Medicine, spoke on prejudice and discrimination toward obese people. He reported that obesity is consistently viewed as a moral problem associated with being lazy and indulgent, despite studies on genetics, leptin, and external influences on weight. Obese people receive lower pay than non-obese people for the same jobs, are less likely to be selected as tenants of apartments, and are more likely to be depressed. A person with a BMI over 40 has almost five times the risk of depression than a non-obese person. Dr. Wadden said this depression is partly caused by the pain associated with the extra fat. Discrimination against the obese occurs in health care professionals as well. In a survey in which 12% of physicians responded nationwide, 62% reported that obese people are awkward, 53% called them unattractive, 51% said they are noncompliant, 50% reported them to be ugly, 44% called them weak-willed, and 35% called them sloppy. Keep in mind that the self-selecting aspect of the study design gives it an intrinsic positive bias. Despite obvious discrimination, there is no protection for obese people under the law. Title 7 prevents discrimination based on race, color, religion, sex, or national origin, but there is no protection against discrimination based on weight or appearance.

Dr. Wadden also discussed practical strategies to help patients achieve successful weight loss. Healthcare professionals should tell obese patients that their initial goal is a 10% reduction in body weight. Patients will be relieved to hear this, since 10% is a more achievable target than a normal BMI. Also, meal replacements are effective because they provide fixed nutritional content. People generally underestimate their caloric intake by 40%, but meal replacements allow people to avoid the consequences of caloric underestimations.

Kathryn Henderson, Ph.D., from the Yale Center for Eating and Weight Disorders, spoke on the social consequences of obesity. She reported that obese people have lower educational attainment, less parental financial support, lower rates of acceptance into college, lower socioeconomic status, wage disparities, lower employment levels, and lower benefits. There are also important gender differences; for example,

obese women suffer more than obese men in the educational domain. Obese women earn an average of 12% less than non-obese women. Employers rate obese job applicants has having poor self-discipline, lower supervisory potential, poor personal hygiene, less ambition and productivity, and judge them as being more appropriate for jobs with little face-to-face contact with the public. Doctors, nurses, medical students, and mental health providers self-report that they hold negative views toward obese people. Thirty-one percent of nurses say they "prefer not to care for obese patients;" 24% say they are "repulsed" by them, and 12% of nurses say that they "prefer not to touch obese patients" at all.

The implications of discrimination against obese people are frightening. Dr. Henderson reported that the quality of life in obese children is comparable to the quality of life in pediatric cancer patients. Obese women are less likely than non-obese women to obtain preventive health services, and more likely to cancel or delay appointments. This puts obese women in an especially bad place, since they are much more likely to suffer health problems than non-obese women. Two-thirds of obese patients say that most doctors do not understand how difficult it is to be overweight. Dr. Henderson called on us to recognize that obesity is multi-determined, that many obese patients have tried weight loss repeatedly, that small weight losses can result in health gains, and that individuals can be overweight and fit at the same time.

Gastric Bypass—A Quick Cure for Diabetes?

Speakers at this session presented extremely convincing evidence that gastric bypass surgery may cure type 2 diabetes not only in obese people, but also in non-obese people. It has been known for decades that gastric bypass surgery has an antidiabetic effect in obese patients. What has not been known is whether the antidiabetic effect is due to the weight loss or the surgical procedure itself. The findings presented in this ADA session, particularly those from Dr. Francesco Rubino, could fundamentally change scientific understanding about the pathophysiology of diabetes and lead treatment targets in a promising new direction.

Dr. Francesco Rubino from the IRCAD/European Institute of Telesurgery in France presented ground-breaking research that pointed toward the bowel as the source of type 2 diabetes. In Rubino's lab, non-obese rats with type 2 diabetes were split into four groups: one group underwent a gastro-jejunal bypass; a second group underwent a sham operation; a third group was put on a restricted food intake diet; and the fourth group was treated with rosiglitazone. The rats given the gastro-jejunal bypass surgery had improved glucose tolerance compared to the other groups after three weeks and had a 42% reduction in the area under the curve of blood glucose level—almost half the amount of blood glucose! Interestingly, when Rubino performed gastro-jejunal bypass on non-diabetic rats, their glucose tolerance worsened, which provides further evidence that the gut plays a key role in the pathophysiology of type 2 diabetes. Dr. Rubino hypothesized that there is an anti-incretin system that modulates incretin (and thus insulin) secretion, and that this anti-incretin system is overactive in people with diabetes. Perhaps gastric bypass surgery silences the anti-incretin signal. The antidiabetic effect of surgery only occurs when the duodenum and proximal jejunum are bypassed, which takes place in both gastric bypass surgery and biliopancreatic diversion. Gastric bypass surgery has a lower risk of complications than biliopancreatic diversion and can be performed laparoscopically. In light of his results in rats, Rubino said that surgeries involving duodenal-jejunal exclusion may be a valuable treatment option for non-obese humans with type 2 diabetes.

Dr. Randy Seeley from the University of Cincinnati also presented his research findings at this session. Dr. Seeley studies a procedure called "ileal interposition," which involves cutting out a piece of the distal ileum and replacing it in the proximal jejunum. There is no net change in length of the gut, rather just a relocation of one segment. (Think of it as changing the order of a sequence of letters, from A-B-C-D-E to A-D-B-C-E.) This seemingly simple procedure in rats results in reduction of body weight and food intake

compared to rats given a sham operation. As determined by rat feces, this procedure does not cause malabsorption. Dr. Seeley pointed out that both GLP-1 and PYY originate in the distal gut, which in the ileal interposition is cut out and placed higher up in the intestine where it gets more stimulation. Plasma PYY concentration and PYY gene expression rise dramatically in the first two hours after ileal interposition, and there is also a surge in GLP-1 concentration and gene expression in the first forty minutes after surgery. In short, Dr. Seeley demonstrated that ileal transposition improves insulin sensitivity, which implies a connection between GI function and insulin sensitivity.

DRIVING AND HYPOGLYCEMIA: A Recipe for Disaster

Even though we personally think that danger and diabetes are sometimes overstated, it's not the case with diabetes and driving, which was a topic of focus at this year's ADA. Type 1 diabetic drivers have more driving mishaps (percentage-wise!) than type 2 diabetic and non-diabetic drivers. In light of this, it is especially important for people with type 1 diabetes to *always* test their blood glucose level before driving, no matter how short the driving distance; this is in the intermittent era! To us, increased safety associated with driving could be one major benefit of continuous monitoring. We and other patients would very much like, thank you very much, to be warned if our blood glucose is dropping at over 2 mg/dL per minute (that's a straight down arrow on Abbott's Navigator), and would also love to know if blood glucose levels weren't changing much at all – but to be alerted if they are! Overall, we think that once accurate, real-time (reimbursed) continuous monitoring emerges, we'll be far better off on this front. This session on driving and hypoglycemia also emphasized that it is crucial for healthcare providers to speak to their patients about this matter. Dr. Katie Weinger from Joslin Diabetes Center reported that over half of driving mishaps in diabetic drivers were not discussed with their doctors, and Dr. Brian Frier from Scotland called the issue a "major education problem among individuals with diabetes and health care professionals." Some key points from the ADA session on driving and hypoglycemia include:

- Dr. Frier discussed the association between hypoglycemia and driving. He reported that the frequency of mild hypoglycemia in diabetic patients does not change over a twenty-year period, but rather stays constant for them at about two episodes per week. In contrast – and importantly – *the frequency of severe hypoglycemia increases steadily over time*, such that the longer a person has diabetes, typically, the higher his or her risk of having an episode of severe hypoglycemia, due (we imagine) to increases in hypoglycemic unawareness. At the same time, awareness of hypoglycemia (symptoms such as sweating, shaking, and trembling) declines with time. He noted that impaired awareness of hypoglycemia affects 25% of adults with type 1 diabetes.
- Dr. Frier also provided some guidelines regarding driving and hypoglycemia. Cognitive function deteriorates at blood glucose levels less than 54 mg/dL, and driving becomes impaired at 68 mg/dL. Cognitive function does not recover fully until 40–90 minutes after the blood glucose level returns to normal. Based on this data, Dr. Frier recommended that a person with diabetes wait at least 45 minutes to begin driving after having a hypoglycemic event. (What an inconvenience to wait 45–90 minutes; we believe most patients don't do this, but based on this research, they should!) Interestingly, it turns out that driving has a significant metabolic demand; who knew that we burn calories while driving?! Therefore, a person with diabetes should measure his or her blood glucose level before driving and eat a snack if it is lower than 90 mg/dL.
- Following Dr. Frier, Dr. Katie Weinger of the Joslin Clinic gave another talk on driving and hypoglycemia. First, she provided background information based on a cross-sectional, international, multicenter retrospective study published in *Diabetes Care* in 2003. Researchers conducted the study at diabetes clinics in seven U.S. and four European cities, where people with type 1 diabetes, type 2 diabetes, and nondiabetic spouse control subjects (n = 313, 274, and 326, respectively) completed anonymous questionnaires on driving. This study demonstrated that type 1 diabetic drivers are at a higher risk for driving mishaps than type 2 diabetic drivers and non-diabetic drivers, with type 1 diabetic drivers reporting significantly more crashes, moving violations, and episodes of

hypoglycemia than type 2 diabetic drivers or spouse control subjects (P < 0.01-0.001). The use of insulin or oral agents in type 2 diabetic drivers did not alter their driving mishap rates, which were similar to the rates among non-diabetic spouses, which somewhat surprised us but reinforces that hypoglcyemia is less of a problem overall in type 2 patients – even though average control is just as bad or worse.

- After presenting the findings that hypoglycemia puts drivers with type 1, not type 2, diabetes at an increased risk for driving mishaps, Dr. Weinger discussed a recent prospective study of 550 drivers with type 1 diabetes. The results from the study demonstrated that women are less likely than men to drive during an episode of hypoglycemia, and young people are less likely to drive while hypoglycemic than older drivers.
- It was underscored throughout the session that healthcare providers do not discuss hypoglycemia and driving nearly enough with their diabetic patients; in the first study, half of the type 1 diabetic drivers and three-quarters of the type 2 diabetic drivers reported never discussing hypoglycemia and driving with their doctors and CDEs. How bad is that?! Can we say, "conflict avoidance"?!
- In short, this session strove to emphasize that in order to protect all drivers, diabetic and non-diabetic alike, people with type 1 diabetes need to measure their blood glucose levels before driving and at least every two hours during long drives. Their blood glucose levels must be high enough to cover for the metabolic demands of driving, they should keep snacks in the car, and they must stop driving if they sense hypoglycemia.
- To us, the only thing that was really missing from this session was the absence of any mention of continuous; this new technology, once the accuracy is refined and the products are user friendly, could really help with this major problem of driving and hypoglcyemia. We suspect that future ADA presentations on driving and hypoglcyemia will be more edifying when continuous monitoring offers patients a real alternative. A last clinical implication - what we view as increased focus on dangers of hypoglycemia does bode well, we think, for Diobex, which to our knowledge is the only company developing a therapy for *prevention* of hypoglcyemia – such a drug combined with continuous monitoring would be quite a combination.

A TOUR OF THE DEVICE COMPANY BOOTHS

Exhibit Review: CGM, SMBG, and CSII devices at the ADA

From our perspective, the *newest* news from this year's ADA focused more on drugs than devices, as indicated in our piece above. BUT that doesn't mean there was no device news –far from it! With a total of nearly 20 companies with investments in blood glucose monitoring and insulin delivery on the floor, device companies accounted for just 10% of exhibitors. Yet devices commanded significantly more than 10% of floor space or traffic: Grand layouts and compelling attractions worked to stop visitors in their tracks. There's just something about a big booth with a live vocalist (Medtronic), or a medium-sized one lit up with custom neon signs (DexCom) or a booth of any size where a former Miss America is signing autographs (Animas) that makes it hard to pass by without a second glance. We spent significant time at device booths, as we just can't resist demonstrations of the latest diabetes technology, and here are. our gleanings from the device-focused exhibitors at the ADA's 65th Scientific Sessions and Annual Meeting:

DexCom's presence in the Exhibition hall made a real splash at the ADA. With their continuous blood glucose sensor currently under review by the FDA, DexCom was unable to provide product literature at the booth, but there was an engaging short video showing how the product works, as well as two key abstracts in the poster section of the exhibit hall (398-P and 2-LB).

Abbott Diabetes Care also shared information on their continuous glucose monitoring device, the Navigator, also under review by the FDA, and there was an impressive abstract from UVA (abstract 394-P) that showed Navigator strength vs Medtronic CGMS in accuracy, particularly in all-important hypoglycemic levels. Abbott featured their mainstay product line with some new additions. The newest Abbott meter, the Freestyle Freedom, is expected to be launched shortly and will replace the original Freestyle meter that put Therasense on the map. The new Freestyle Freedom has a five-second test time, a large display and four "it's time to check your blood sugar" reminder alarms. Sweet! Abbott is also launching the new Precision Xtra test strip, which has a sample volume almost three times smaller than the previous test strip (0.6μL vs. 1.5μL).

The other SMBG companies focused exclusively on episodic monitoring. LifeScan had an impressive booth featuring the OneTouch UltraSmart, OneTouch Ultra and their newest meter, OneTouch Horizon, which is positioned as a low cost meter for people with diabetes in developing countries. The Horizon was launched in India last year and we understand it is doing some whopping business – excellent to hear this as good technology is a major missing piece in India among other poor countries. Reinforcing their focus on the global epidemic of diabetes, at the booth LifeScan taped real-time impromptu interviews with HCPs answering the question, "What can be done about the global epidemic of diabetes?" Excerpts may appear in Lifescan television spots in coming months. We loved this.

Roche featured two new product offerings at its booth. On the meter side, Roche has the new Accu-Chek Aviva, which received FDA clearance in April 2005. To us, one of the most interesting takeaways from the entire meeting was that Roche is waiting until August, when it expects the Aviva to be on MCO formularies, to *introduce* this meter in the marketplace, which certainly underscores the importance of reimbursement. The Aviva offers a five- second test time, 500-test memory, and a 0.6μL sample size applied to an easy-to-handle test strip. On the lancing front, Roche has the new Accu-Chek Multiclix, an innovative all-in-one lancing device with a disposable drum of six pre-loaded lancets. The device offers different depth settings and has been approved for alternate site testing. This product will certainly make testing more convenient, discreet and faster. We look forward to trying it out!

Bayer featured the Ascensia Contour, its newest meter and test strip system "designed to make accuracy automatic" (excellent line) because each test strip calibrates the meter before every test, bypassing the common, serious patient error of forgetting to recalibrate the meter between vials of test strips. Since most meters on the market today offer convenience, fast testing time, memory and data management capability, Bayer makes accuracy a point of differentiation In a white paper, they claim that coding errors in some meters can skew results by up to 43%. We're not sure patients or providers are particularly focused on this – once it's FDA approved, that seems to be (despite Vioxx) all people care about. We personally care a lot about accuracy in episodic meters ourselves, so we applaud the white paper.

Last for the larger diabetes companies, **Becton Dickinson** featured its BD Logic meter, which in its Paradigm Link incarnation interfaces with Medtronic's Paradigm 512/712 and 515/715 insulin pumps.

Even the smaller players had something new to offer in blood glucose monitoring. **Home Diagnostics, Inc.** offered a preview of its new Sidekick, which is presently awaiting FDA clearance. The Sidekick is a unique disposable meter that is an all-in-one blood glucose testing system, with the meter as the top of the test strip vial. Though it features a competitive 1.0μL blood sample size – like OneTouch Ultra and UltraSmart – and a <10-second testing time, it is being positioned as a value product that offers convenience to the user. In addition, several smaller companies from Asia showcased their meters at ADA as part of their strategy to enter the US market: Where better than the ADA to make a match with a diabetes device distributor?

On the whole, the new products introduced seemed to be incremental improvements to existing technology. The real leap forward will take place when real-time continuous monitoring is available for patients for existing monitoring systems that currently require fingersticks (or arm sticks). Until then and probably after that too, we'll be watching closely what the impact these new products have in the marketplace and how their entries affect market share gains or losses among blood glucose monitoring companies. Noninvasiveness will also be key to watch, particularly as inhaled insulin appears to be increasingly viable.

There is so much buzz about A1C and achieving ADA targets of 7% or lower – and for that matter, more clinicians seem to be talking about reaching the "stretch" targets for patients of 6.5% or below. Interestingly, in an excellent symposium about monitoring sponsored by Abbott, Drs. Bruce Bode and Irl Hirsch polled the audience regarding the average A1C of their patients. While we know only about 30% of diabetes patients in the country are estimated to be meeting glycemic targets, the symposium audience indicated that *their* patients were at goal for the most part! We wonder if perhaps there was an element of self-selection at work in this sample: Perhaps healthcare professionals who have seen that patients can do *well* are more inclined to seek information on helping them do *better*. Or maybe all that glitter?

Metrika is awaiting FDA clearance of its new A1cNow INViEW meter, a next-generation product for point-of-care A1C testing. The new INViEW provides results in five minutes, is a multi-test unit, requires 5 μL of blood, is an all-in-one sampling device and has a larger display screen and higher accuracy than earlier versions. Like Bayer's DCA device and earlier versions of A1C Now, this product offers convenient A1C testing into the physician's office thus allowing HCPs to provide immediate feedback to patients and modify patient treatment at point-of-care; unlike the Bayer DCA, no capital equipment purchase is necessary. As we understand it, accuracy has improved from prior versions, and we certainly support all products that aim to strengthen patient focus on A1C.

Insulin pump and SMBG-integration was the theme at ADA for the pump companies. Medtronic leads the way in this department: CGMS Gold, Guardian (Medtronic's next-generation continuous monitor, which is awaiting FDA clearance) and Medtronic's sensor-augmented pump (still considered investigational) were all featured at the booth. Medtronic had several key abstracts on continuous monitoring (393-P, 399-P, and 409-P). For existing products, **Becton Dickinson's** Paradigm Link meter, a version of the Logic, interfaces with Medtronic's Paradigm pumps. The **Animas** booth focused on the IR 1250 insulin pump and the continuous glucose monitoring IP that Animas obtained through its acquisition of the rights to Cygnus's GlucoWatch G2 Biographer earlier this year. Animas also promoted the Diabetes Heroes campaign that Animas pump-wearer and dLife host Nicole Johnson Baker has launched. **Smiths Medical's Cozmo** booth highlighted the Abbott FreeStyle-based CoZmonitor module that attaches to the pump for automatic blood glucose value transmission (the Paradigm Link meter communicates with Medtronic pumps via radio frequency; compared to that technology the CoZmonitor may offer more reliable data transmission). Smiths representatives are excited about the impending launch of the Cleo infusion set, scheduled for the AADE meeting in DC this August. Lastly, **Insulet** did not have a booth, despite having an approved product – we'll be watching at AADE for their entry as well.

–by Melissa P. Ford, Katelyn L. Gamson, Olayinka A. Olowoyeye, Andrea B. Stubbs, and Kelly L. Close

2. Literature Review

***NEJM* Alert! A very interesting *NEJM* study and editorial came out during ADA that focused on gestational diabetes mellitus (GDM). If the June 16 *NEJM* is sitting on your desk(top), flip to "Gestational Mellitus – Time to Treat" by Michael F. Green, M.D., and Caren G. Solomon, M.D.,**

M.P.H. Green and Solomon do an excellent job of cutting through the clutter of studies on GDM to make one thing clear: there is currently no consensus on the usefulness of screening and treatment for GDM, but the study in this issue of *NEJM* may soon change that. GDM is a common (*increasingly* common: over 135,000 cases per year), yet highly debated disorder, defined as glucose intolerance that begins during pregnancy or is first diagnosed during pregnancy.

Historically, data on the effectiveness of screening for and treating GDM has been inconsistent and inconclusive. In its most recent guidelines, the US Preventive Services Task Force stated that "evidence is insufficient to recommend for or against routine screening for gestational diabetes." Likewise, the American College of Obstetricians and Gynecologists (ACOG) admits that there is no solid evidence supporting screening for or treating GDM, while officially recommending GDM management. Important questions remain unanswered: does GDM pose serious risks to the developing child? If so, does treatment attenuate those risks? The incidences of fetal macrosomia, birth trauma, and Caesarean delivery are all increased with GDM, but these complications rarely result in permanent injury, and it is not clear whether interventions to lower glycemia in pregnancy reduce the risks of these complications. The authors of this article initially provide two reasons against treating GDM: 1) gestational diabetes has not been clearly linked to perinatal mortality; 2) no existing long-term data shows whether treatment reduces other risks associated with GDM, including obesity and type 2 diabetes in the child. Caesarean delivery brings up another issue: it has been suggested that a diagnosis of GDM lowers the threshold for Caesarean delivery, and the resulting morbidity from Caesarean delivery may outweigh the benefits of screening for and treating GDM.

Now for the big news you've been waiting for: in this issue of *NEJM*, Crowther, et al. published their results from a large (n = 1000), randomized, multicenter trial of treatment for gestational diabetes. Women between 24 and 34 weeks' gestation were given a 75 g oral glucose tolerance test, and those with glucose values below 140 mg/dL after an overnight fast and between 140 and 198 mg/dL at two hours were eligible for the study. The 490 women randomly assigned to the intervention group were given individualized dietary counseling, taught to monitor their blood glucose levels, and provided with insulin to maintain fasting and pre-meal glucose levels below 99 mg/dL and two hour postprandial levels no higher than 126 mg/dL. This treatment was consistent with the approach used in facilities where screening and treatment for GDM are routine. The 510 women randomly assigned to the control group received routine care, similar to the care given in facilities where screening and treatment for GDM are not routine.

Results dramatically favored screening and treatment. The offspring of women in the intervention group had a much lower risk of a composite primary outcome measure (including perinatal death, shoulder dystocia, bone fracture, and nerve palsy) than the offspring of mothers in the control group (1% vs. 4%; adjusted relative risk, 0.33; 95% confidence interval). While there were five deaths among the offspring of mothers in the control group, there were no deaths in the intervention group. Macrosomia was significantly more common among infants of mothers in the control group than among infants of mothers in the intervention group (21% vs. 10%, $p < 0.001$). Contrary to expectations, the rates of Caesarean delivery in the two groups were comparable (31% in the intervention group and 32% in the control group). Maternal postpartum mood and quality of life, measured in a segment of the women, was better in the intervention group than in the control group, which suggests that frequent monitoring and consultation during pregnancy did not negatively affect the maternal quality of life.

This study by Crowther and colleagues provides much needed evidence demonstrating that screening for and treating gestational diabetes can lower the risk of perinatal morbidity without increasing the rate of Caesarean delivery. Green and Solomon mention that two studies are in progress to assess glycemic control in pregnancy: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) is evaluating the relationship between glycemia and perinatal outcomes, and another trial is evaluating the effects of tight glycemic control in pregnant women who receive a diagnosis of GDM based on having normal fasting

glucose levels but an elevated glucose level at two points in time after a 100 g oral glucose load. We do note one concern: everyone seems to be using different diagnostic screening tests. In this article alone, we saw four different sets of criteria: one from Crowther et al., one from the HAPO study, another from a different ongoing study, and another given by the American College of Obstetricians and Gynecologists. Now that the trial by Crowther, et al. has provided a convincing reason to screen for and treat gestational diabetes, we are waiting for solid criteria on when to treat. And we'll have more on screening to follow; it seems that if we can get it right, this is an area of much opportunity, where the public health implications could be enormous, indeed.

–by Katelyn L. Gamson

3. More news of note!

- **Novo's Levemir approved** – see our weblog on this at www.closeconcerns.com - more will be up in the coming couple of days
- **New obesity partnership** – Matabasis and Merck – see our weblog at www.closeconcerns.com
- **Medtronic M&A Update –** We wrote about the creation of Medtronic Obesity Management just last month and sure enough, the company announced a few days ago the acquisition of Transneuronix, a gastric pacing company – see our blog at www.closeconcerns.com

–by Melissa P. Ford and Kelly L. Close

4. Conference Preview

- **AADE** meets in Washington, DC August 10–14; information is on-line at www.aadenet.org.
- **The Obesity Drug Development Summit** will be held July 21–22 in Arlington, VA. On a long of interesting talks are sessions regarding the potential of 11b HSD inhibitors, potential targets affecting fatty acid oxidation, and Dr. Eric Colman (FDA) on current regulation of obesity drugs and what will impact revisions to obesity drug development guidelines. Information is online at http://www.cbinet.com/show_conference.cfm?confCode=HB549
- **EASD** is in Athens this year, September 9–15. We understand that for this meeting, EASD received 2313 abstracts for review, a record number, up 15% from last year. To boot, US and Asian submissions have risen 25%. The full program is now available for downloading (PDF) from the EASD website http://www.easd.org . Check it out: there is also a two-day satellite symposium on the history of diabetes, which will take place September 7–9 in Delphi. Co-chairmen of the Symposium will be Professor C.S. Bartsokas and S.G. Marketos. The purpose of the symposium is to cover historical aspects of diabetes from ancient periods to the last century, throughout the world. Lectures will concentrate on discoveries, physicians of the past, texts, history of associations, journals and books on the history of diabetes. Is that *excellent*??!
- **NAASO (The North American Association for the Study of Obesity – www.naaso.org)** meets in Vancouver, British Columbia, October 15–19.
- **The Diabetes Technology Society** meeting takes place in our fair city by the bay (www.diabetestechnology.org) November 10–12

–by Melissa P. Ford, Leah Edwards, and Kelly L. Close

Diabetes Close Up is a newsletter highlighting notable information and events related to selected companies with diabetes/obesity businesses. This newsletter is put forth as an unbiased commentary on the industry. If you have any suggestions or comments regarding content, please contact info@closeconcerns.com. If you would like to 1) unsubscribe; 2) add a name to the DCU mailing list; or 3) offer any suggestions or comments regarding content, please write to info@closeconcerns.com.

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