

DIABETES CLOSE UP

Diabetes Close Up
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“Meet you at the quilt ...”

The Shorter Version

From the Editor:

“Meet you at the quilt...” The ADA starts June 10 in San Diego. Exciting! As ADA approaches, far-flung colleagues will say to you, “Do you want to meet at ADA?” You’ll find yourself saying, you know this, “Sure, let’s have breakfast Saturday? ... Oh right, there’s that great symposium, I definitely do not want to miss hearing Dr. Henry... hmm, coffee Friday? ... I will definitely need it, even on day one - oh, but right, I forgot about stressing out the beta cell. Do not want to miss that. ... No, no, not only do I not want to miss it, I cannot miss it. ... Coffee later Friday? ... Yes, okay, great. 4:30 on Friday.... Where should we meet? Okay, at the Novo booth. I wonder if it’ll be as impressive as last year’s booth!? Will it have an upstairs? I can’t wait for detemir ... Oh, right, the exhibits aren’t even open yet Friday, are they? I always forget that. Where should we meet? The posters? Oh right, they aren’t open yet either. And how would we know what row?... Right, right, what area, even! Did you see all the posters are up all three days? ... I know, I know, that is excellent, you’re right. Okay, at the exhibit door is where we should meet? Okay good. ... Oh, which door? ... The north door? Which one is that? ... The one on the right side? Which right side? ... Right, scrap that. Okay, the registration booth? Which registration booth...? Meet at the hotel? I won’t want to walk back. But, where are you staying ...? ... What do you mean, you don’t have reservations yet? ...”

THIS year, the place to meet will be by the quilt. That is the Children With Diabetes Quilt for Life, which will be on the same floor as registration and exhibits – it has one entrance and it is the standout meeting place from our perspective. This is a most excellent setting, and if you are early, you will have plenty to see. This quilt is a powerful collage of the lives of over 400 people living with type 1 diabetes whose families have each contributed a three-by-three-foot panel to this ever-growing public-awareness project. Learn more about it at <http://www.childrenwithdiabetes.com/activities/quilt>

Back to ADA ... there are many excellent sessions of note as we said in our April DCU – check out your online scheduler now. In the meantime, take good care and we look forward to seeing many of you in southern California soon!

–by Kelly L. Close

Conference issue – One DCU, 10 meetings. Selected highlights from diabetes and obesity conferences and meetings around the world. Literally.

- **#1: American College of Clinical Endocrinologists – Washington, DC – May 18–22.** First, at a press conference we learned that the “state of diabetes in America” could be summarized in one word: *dismal*. As a result of the meeting, we now know more about Byetta, muraglitazar and several other potentially blockbuster, or at the very least noteworthy, compounds – *page 3*
- **#2: UCSF Eighth Annual Teaching Center Patient Symposium – San Francisco, CA - May 21.** A room full of UCSF experts discussed new technologies and therapies, all for the benefit of

- patients – proof positive that, if one must be a PWD, San Francisco is a good city in which to be one. – *page 5*
- **#3: Pediatric Academic Societies – Washington, DC – May 14–17**, A snapshot of two significant contributions to the proceedings – one arising from Dr. Francine Kaufman’s clinical expertise, the other stemming from the poster “*Continuous Subcutaneous Glucose Monitoring in Pediatric Type 1 Diabetes: A Single-Blind, Randomized Controlled Trial*,” submitted by Lagarde and colleagues from UNC–Chapel Hill – *page 6*
 - **#4: 10th World Congress of the International Pancreas and Islet Transplant Association – Geneva – 4–7 May, 2005**. Of course we still hope for a cure. Here we highlight two rather divergent perspectives on how insulin independence might best be pursued – *page 7*
 - **#5: IV International Assisi Symposium – Assisi, Italy – April 28–May 1, 2005**. This meeting was terrific. With sessions ranging from the nearly scandalous to the certainly scintillating, we didn’t get much sleep despite Assisi’s serenity – *page 9*
 - **#6: Diabetes UK – Glasgow – April 20–22, 2005**. The UK is an excellent place to visit (especially Glasgow) but a bad place to live - with diabetes. Yet, progress is being made... - *page 12*
 - **#7: Clinical Diabetes Technology – San Francisco, CA – April 15–16, 2005**. Day one: continuous glucose monitoring. Day two: insulin delivery strategies. Did we have to think twice, or even *once*, about attending?! - *page 18*
 - **#8: American Heart Association Research Roundtable Luncheon – Palo Alto, CA –April 14, 2005**. Observations from Stephen Blair of the Cooper Institute regarding today’s obesity-inducing American lifestyle and what we can do about it – *page 21*
 - **#9: “New Frontiers in Monitoring: Brave New World – But – What to Do with the Data?” – Boston, MA – March 19, 2005**. Boston Diabetes Expo debate between Drs. Howard Wolpert and David Nathan – *page 22*
 - **#10: EASD Study Group on Artificial Insulin Delivery and Pancreas and Islet Transplantation – Igls, Austria – January 23–25**. Notes from the cutting edge of European research into insulin therapy and beta-cell replacement – *page 25*
2. **Conference preview – Endocrine Society, ADA, AADE, Obesity Drug Development Summit, EASD, NAASO and more ...** – *page 27*
 3. **More news of note!** – *page 27*
 - **Roche Update** – Thanks to the recent Roche diagnostics review, Diabetes UK and AACE, now we know much more about the product pipeline, notably Aviva and Spirit, the new blood glucose monitor and pump – *page 27*
 - **OmniPod Update** – We think with this innovative pump entry, the market will continue to expand, benefiting the company and the entire industry – *page 30*
 - **Medtronic Earnings Call** Three items got our attention: the acceleration in diabetes sales, the drive toward continuous, and the creation of Medtronic Obesity Solutions - *page 30*
 - **Sanofi-Aventis Earnings**. Lantus, Acomplia, and Apidra updates ~ *page 30*
 4. **Errata and Etc.** – *page 33*

The Longer Version

1. **One DCU– 10 meetings!** So many things happen simultaneously in the wide worlds of diabetes and obesity that we have run short of time and space for publishing conference reports in the past few months. We hope you will enjoy the following selections from our notes, which represent our take on *highlights* only. We hope we've captured views correctly – we write, as always, from the perspective of interested patients, rather than from that of trained HCPs, and if we've missed something, we'll report back. If you'd like more than these highlights on conferences, we will publish our *Diabetes 2005 Roundup* after ADA, which will contain our detailed notes from conferences we've attended over the past year as well as a number of focus pieces on what we're calling "Generation 2005" drugs, other new products, milestones to watch for in 2006, and more. For a glimpse into the format of *Diabetes 2005 Roundup*, you are welcome to download information from our *Diabetes 2004 Roundup*, from our website, www.closeconcerns.com.

- **#1: American Association of Clinical Endocrinologists – Washington, DC–May 18–22, 2005**

This year's AACE meeting was subtitled "Advancing the Standards of Endocrine Care: Putting Science into Practice" with good reason: even the corporate sponsored symposia (of which there were rather more than in previous years – nearly 20 in all!) were devoted primarily to currently available therapies rather than potential ones. As one might have expected a few weeks before the ADA, most new data was saved for June in San Diego (muraglitazar excepted) and the mood in the exhibition hall was low-key – except at the Roche, Amylin, and Amylin/Lilly Alliance booths. AACE functioned as the debutante conference for three highly anticipated products: the Roche Accu-Chek Spirit insulin pump; Amylin's Symlin (pramlintide); and, with great rejoicing, Amylin and Lilly's Byetta (exenatide). Below are our top picks from five action-packed days of AACE. The complete program may be downloaded from <http://www.aace.com/2005/>

 - Tuesday: The State of Diabetes in America press conference, featuring Surgeon General Carmona, entertainer and GSK spokesperson Della Reese, and Drs. Lawrence Blonde (Ochsner Clinic Foundation, Louisiana), Paul Jellinger (ACE President; University of Miami); and Jaime Davidson (UT-Southwestern). (<http://www.stateofdiabetes.com/>)
 - The State of Diabetes in America report is the culmination of nearly 156,000 telephone surveys of patients with type 2 diabetes from all 50 US states. The results are sobering: in keeping with Dr. Carol Koro's findings, published in *JAMA* 2004, two-thirds of US type 2 diabetes patients have A1C levels over 6.5%. Unbelievably, the interviewers learned, 61% of the respondents did not know the meaning of "A1C test" on the first pass; even after being told by an interviewer, 51% couldn't remember their last A1C result.
 - The *really* frightening part was that fully 84% - 84%! - of respondents thought they were doing a good job of managing their diabetes by controlling their blood sugar.
 - Wednesday: "So why are there skinny pot smokers?" asked an audience member after the Sanofi-Aventis symposium "Managing Metabolic Imbalance via the Endocannabinoid System" that was devoted to rimonabant (Acomplia), the endocannabinoid receptor blocker the company has in development. In case you're wondering, skinny pot smokers are probably small but unfit, according to the symposium faculty, comprised of Drs. Michael Jensen, F. Xavier Pi-Sunyer, and Louis Aronne. According to the two-year RIO-North America study data disclosed, 62.5% of study completers lost >5% of their original body weight; 30% of completers lost >10% body weight. We'll be looking for more information at ADA on who didn't complete and why. Also, we learned that while rimonabant should be first-in-class, at least six other companies have endocannabinoid receptor blockers in development. Obesity is big (so to speak) – just check out the ADA schedule, which has literally over a dozen related sessions and multiple posters planned.

- Thursday: Tensions between GlaxoSmithKline and Takeda/Lilly over GSK's Avandia (rosiglitazone) vs. Takeda's Actos (pioglitazone) became palpable at a breakfast (read: 6 a.m.) symposium. Head-to-head data has shown that as monotherapy, Actos mitigates lipids, though not as much as a TZD plus a statin would reduce LDL and triglycerides. Yet, if taken as monotherapy for hyperglycemia, Avandia significantly *raises* levels of "bad" blood fats. It's a good thing that the ADA Clinical Practice Recommendations specify combination therapy incorporating a statin when a TZD is prescribed for a patient with disordered lipids; that guideline is the leg that GSK has to stand on here.
 - The data...

Results summary	Actos change from baseline	Avandia change from baseline	P value between groups
A1C	-0.7	-0.6	P=NS
Triglycerides	-12.0%	+14.9%	P≤0.005
HDL-C	+14.9%	+7.8%	P≤0.005
LDL-C	+15.7%	+23.3%	P≤0.005
LDL particle concentration (nmol/L)	-50.5	+110.5	P≤0.005
LDL particle size (nm)	+0.5	+0.3	P≤0.005
Non-HDL-C (mg/dL)	+3.6	+25.7	P≤0.005
Apo B (mg/dL)	-0.2	+10.6	P≤0.005

- But Actos is not completely off the hook. At AACE, BMS released new data on muraglitazar. Drs. Cindy Rubin and Bob Friederich from BMS presented two posters data comparing its Phase III dual-PPAR agonist compound muraglitazar (no brand name yet) with pioglitazone. See www.bms.com for the detailed press release. In this (deep breath) double-blind, randomized, 24-week clinical trial in 1,477 drug-naïve patients with type 2 diabetes who had inadequate glycemic control with use of a diet and exercise regimen, muraglitazar data didn't look bad. In fact – and this *wasn't* noted in the press release – the compound had a very significant A1C impact at the 20mg dose – a drop of 1.7 points over 24 weeks, from a relatively low baseline of ~8. Yes, you're right, since they didn't include this in the press release, adverse events were much higher at this dose – the poster stated that 45% of those taking the 20 mg dose had treatment-related AEs, while the 1.5 mg and 5 mg groups both had 22% related AEs. Unfortunately, it was difficult to get significant elaboration on side effects.
 - A1C goals (poster 760): within 24 weeks, 1.5 mg of muraglitazar got 29% of patients to the ACE target of ≤6.5% and 5 mg of muraglitazar got 43% of patients to ≤6.5% in 24 weeks – while 15 mg of pioglitazone got 24% of patients to ≤6.5% in the same period of time. 1.5 mg of muraglitazar looked comparable to 15 mg of pioglitazone in terms of A1C reduction, but a 5 mg dose of muraglitazar was more impressive in terms of A1C drop, although it depends how the adverse events look in large numbers and after a longer period. Indeed, we would look for this compound to have an *extensive* safety review.
 - Lipids (poster 866): at 24 weeks, 2.5 mg of muraglitazar had reduced triglycerides by 18%; 5 mg caused a 27% reduction. In the open-label 5 mg muraglitazar group, triglycerides dropped by 31%. Meanwhile, placebo takers' triglycerides increased by 2%. HDL was increased by 10% with 2.5 mg muraglitazar over 24 weeks and by 16% in the 5 mg dose group. The open-label 5 mg group realized a 12% increase in HDL. The placebo takers' HDL rose by 2%, as had their triglycerides. (CC Note: It is still too early to call, and as noted, many will want to see more on safety, but from data seen so far, muraglitazar might be indicated for monotherapy in selected patients whose blood glucose levels are worse than their lipids; patients who are in less need of a statin than many patients for whom an oral hypoglycemic agent is required. It won't be a panacea,

but could be promising for some, depending, again, on the risk of adverse events.) Will be interesting to see longer term data on lipids as the quest continues to find a pill that addresses both glycemic and lipid abnormalities – as noted, the ADA Clinical Practice Recommendations state that patients with diabetes should be on both blood sugar-lowering medication and a statin: no single pill is currently indicated for both. The corporate-sponsored symposium for clinicians focused on the rationale for developing a dual PPAR-agonist but did not have new information on muraglitazar.

- Incidentally, it really seems to us like some of this stuff should be standardized - the hypoglycemia definition for this work was <50 mg/dL, and must *confirmed* by fingerstick – very liberal definition of hypoglycemia (like, with that kind of definition, will any hypoglycemia even show up?)
- Friday was all about Amylin, in our view. The company’s corporate symposium was standing room only and all 500 copies of the syllabus were *gone* five minutes before the program began. We’ll take it on faith that anyone interested in new diabetes drugs has been following the story of Amylin’s Byetta (exenatide); if you need a primer, do visit <http://www.byetta.com> and check out our free DCU supplement “*The Excitement Called Byetta*,” at <http://www.diabetescloseup.com>
 - Questions after AACE presentations, in our view, offered great insight into the minds of prescribing clinicians. Below are the best questions of the evening, answered with aplomb by Drs. David Kendall, John Einhorn, and John Buse. We paraphrase:
 - Q: Are there concerns about DPP-IV inhibition in comparison to this approach? DPP-IV inhibition is not physiological. Could there be a problem with that?
 - A: Buse: DPPs within the body have crosstalk. The companies working on DPP-IV inhibitors (CC Note: Read: Novartis, among others) are being very careful to target the DPP-IV specifically and not to target something that should not be inhibited because of potential immune system implications (CD36).
 - A: Einhorn: It remains to be seen whether weight loss can be obtained from DPP-IV inhibitors. Einhorn asked what would be more compelling to patients: a pill that does not cause weight loss or an injection that is associated with weight loss?
 - Q: Regarding off-label uses....
 - A: Kendall: At a recent meeting with PCPs, there were questions about using exenatide in type 1s and pre-diabetes, using exenatide with TZDs, using exenatide with insulin, and using exenatide in gestational diabetes. There is great interest in off-label use, although for now, the drug is clearly labeled for those failing oral therapy. (CC Note: Unfortunately, in terms of the new state-by-state data from the “State of Diabetes” report, this market looks like it’s in no danger of slowing growth.)
 - Q: How high or how low should the A1C be for me to prescribe exenatide?
 - A: Kendall: The best test of efficacy is whether you are getting to goal (CC note: see above). There is no absolute starting point. Glargine vs. exenatide data will be shown at ADA. Baseline A1C was not an indicator of potential result of therapy.
 - A: Buse: Exenatide flattens the post-prandial hyperglycemic peak. There is no safety data on using exenatide in combination with insulin.

• **#2: UCSF Diabetes Patient Symposium – San Francisco, CA, May 21, 2005**

One of the University of California at San Francisco (UCSF) Diabetes Center’s best aspects is excellent, call-it-outstanding, patient education. This year marked the Eighth Annual Teaching Center Patient Symposium. Get this: this day was actually designed for patients to speak to the experts – and so they did. We believe we’ll continue to see more and more teaching like this as exciting new therapies are developed and made available – a wonderful way to teach and engage patients.

- To start, powerhouse CDE (she really knows what she is talking about!) Gloria Yee discussed “New Technologies for Glucose Testing,” and focused in particular on continuous monitoring. She showed the sensor-augmented insulin pump by Medtronic MiniMed, Abbott’s Navigator and discussed currently available technology such as blood glucose data-management software that can compute standard deviation. It’s sessions like these that really make us believe we are getting ready for a phenomenal change in patient management once continuous glucose monitoring is in-hand.
 - Dr. Chris Freise spoke on “Pancreas/Kidney/Islet Cell Transplant” – this doesn’t seem ready for prime time, but hearing the update on progress appeared to inspire many patients in the room.
 - Dr. Stephen E. Gitelman discussed “Type 1 and 2 Diabetes Screening and Prevention,” where the focus certainly seems to be on finding undiagnosed patients and getting them treated earlier and more aggressively.
 - Dr. Umesh Masharani gave a talk on “Future Therapies,” highlighting GLP-1 in particular and noting that he felt the therapy would be very useful for a wide range of type 2 patients.
 - Diabetes psychology expert and CDE Dr. William H. Polonsky the Great spoke on “Diabetes Burnout: What To Do When You Can’t Take It Anymore.” His talk was straight and you had better believe, if you know anyone who’s a bit down and out about having diabetes, his is a great book to give (talk about a great ROI...).
 - Dr. Renee A. Reijo Pera spoke on “Stem Cell Research.” Things are happening incredibly quickly here and we were genuinely pleased to see UCSF’s involvement stem cell research and just hope the government doesn’t put a screeching halt on innovative work being done.
 - Dr. Elizabeth J. Murphy, MD and CDE + pharmacist Lisa Kroon spoke on nutrition and alternative therapies. The weight loss discussion was excellent but unfortunately we knew the answer going in: the only to lose weight is to eat less and exercise more – attendees guessed they would have to get “back on the bike...” Now if we could just bottle motivation ...
 - Just imagine if you were a patient: wouldn't you love an update like that? And if you are a patient: don't you wish you'd been there?! We were extremely lucky to be in the same room with such devoted experts and that sentiment was shared by the entire audience. Days like this one bode well for better diabetes self-management and we'll be sure to alert you early next year the date of this terrific session.
- **#3: Pediatric Academic Societies (PAS) meeting – Washington, DC – May 14–17, 2005**

Dr. Francine Kaufman (past president of ADA; Professor of Pediatrics at the Keck School of Medicine, University of Southern California; Head of the Center for Diabetes, Endocrinology and Metabolism at Childrens Hospital Los Angeles) presented a potential theoretical model for providing pediatric diabetes care through collaboration between pediatric primary care providers and pediatric endocrinologists. In her prospective model, she defined the following responsibilities and systems for patient care:

- Endocrinologists: responsibility for initial care, yearly evaluation, status review, goals review
- Primary care providers: responsibility for interim visits, routine care, preventative care, assessment of family/work situations
- Common/shared responsibilities: targets for A1C, blood glucose, blood pressure, lipids, sick day management, electronic recordkeeping, standardized protocols, implementing new technologies, reviewing process, research protocols, co-management for hospitalizations (CC Note: And people ask why diabetes is so complicated...?)
- Kaufman advocated a Web-based communication portal to facilitate better communication among patients and their families, primary care providers, and diabetes specialists
- Pilot version being developed by Cerner Information Systems (Kansas City, MO)
- Kaufman proposed that training for pediatric generalists include more diabetes education

- As better diabetes care does not come for free, Kaufman also described a new model for reimbursement, involving the following aspects:
 - Pay for performance: concern about shared risk may be a great deterrent
 - Use of a treatment initiation rate, which covers in- or outpatient initiation of therapy and daily patient contact for one month and weekly contact for two months as well as the yearly rate, which covers one endocrinologist visit and three pediatrician visits; Kaufman suggested electronic transmissions of visit records from the pediatrician's office to the endocrinologist's office to increase the value of patient-specialist contact

PAS featured an intriguing abstract: "Continuous Subcutaneous Glucose Monitoring in Pediatric Type 1 Diabetes Mellitus: A Single-Blind, Randomized Controlled Trial," submitted by Dr. Lagarde and colleagues from UNC-Chapel Hill. We found this abstract important because it focused on CGMS outcomes, not solely on the safety/tolerability/accuracy of the CGMS. Key details:

- Design/methods
 - 27 children (12 male) with type 1 diabetes participated in this single-blind randomized controlled pilot study. Ages: (11.4yrs, mean). Randomization: treatment group (n=18) or control group (n=9). All wore the CGMS for 72-hour periods at zero, two, and four months. Each participant maintained a log that included SMBG data, insulin doses, hypoglycemic events, activity, and diet.
 - A1C tested at zero, two, four, and six months. Adjustments in therapy for the treatment group were based on CGMS and SMBG data, while only SMBG data were used for the control group. A1C change score (CS), defined as the difference in A1C from zero to six months, was compared between groups.
 - Results
 - All participants completed, no adverse events. HbA1c decreased from 8.4% ±0.98 to 7.8% ±0.88 and 8.8% ±0.86 to 8.5% ±0.95 in the treatment and control groups, respectively. The CS was -0.61 ±0.68 for the treatment group and -0.28 ±0.78 for the control group ($p = 0.13$).
 - Conclusions: trend towards improved metabolic control for children with type 1 diabetes managed using CGMS and SMBG data versus those managed by SMBG data alone. We are curious about quality of A1C as well and the extent to which less variability as a stated goal gains more momentum in the coming months.
- **#4: 10th World Congress of the International Pancreas and Islet Transplant Association (IPITA) – Geneva, Switzerland – May 4–7, 2005**

A conference oriented towards basic researchers and clinicians actively investigating curative strategies for type 1 diabetes is both an inspiring and a dispiriting experience: there's so much fascinating, creative, even ingenious research ongoing, but in our view (we are impatient patients) we remain fairly far from an outright cure. IPITA 2005 attracted about 300 dedicated transplant surgeons, cell biologists, islet isolation experts, immunologists, and clinicians overseeing patients in clinical trials related to pancreas and islet transplantation. Below are our synopses of two key sessions – the complete conference program is available at <http://www.ipita2005.org>.

 - **Dr. David Harlan** (NIH) offered a thorough overview of the challenges and benefits of clinical islet and pancreas transplantation in his presentation, **"Unresolved Issues: pitfalls and drawbacks in clinical islet cell transplantation."**
 - Islet transplantation has made "quantum leaps forward" in the past several years, but the challenges still to be overcome are daunting. The supply of donated islets suitable for transplantation is severely limited; immunomodulation/immunosuppression therapies are

not ideal, causing a long list of side effects including toxicity to the kidneys and perhaps also the transplanted islets; and graft survival rates are still low.

- Beyond those familiar issues, Harlan emphasized that we lack sufficient tools to measure islet or pancreas health post-transplant: the first sign of a failing graft is hyperglycemia. Technologies to assess islet health *in vivo*, especially imaging techniques, should be advanced, and the portal vein of the liver, the most common site for islet graft infusion, may not be the best location – perhaps islets do not revascularize well because the environment is not ideal.
 - In addition to severe post-transplant complications, the known and unknown dangers of suppressing the immune system makes beta cell replacement via either pancreas or islet cell transplant appropriate for only a small minority of type 1 diabetes patients. Harlan said, “I don’t regard the immune system as a vestigial organ.”
 - Before arranging for a transplant, Harlan suggested that prospective recipients be referred to an endocrinologist who does not advocate islet cell transplantation, postulating that many patients are in poor control not because their diabetes is inherently uncontrollable, but because their insulin regimen is not optimized.
- **Dr. Shinichi Matsumoto** from the Transplantation Unity of Kyoto University Hospital, Japan, whose team performed the **first living related donor islet cell transplant** in January of this year, presented the case study at IPITA. You might have read of this event in the newspaper, heard something on the radio, or seen a news posting about it on the Web. Further details from the man himself....
- The young woman who received the transplant became diabetic at age 15 as a long-term consequence of pancreatitis onset at age four. Matsumoto explained in detail the significant internal review board requests that he had to fulfill to ensure that the protocol was well conceived.
 - He recruited several Japanese surgeons and researchers working primarily in the US to return to Japan to help with the procedure, as well as Dr. James Shapiro from Edmonton.
 - Stunningly, Dr. Matsumoto’s team extracted 408,144 islet equivalents – approaching the same number of islets usually obtained from a *whole* cadaver pancreas – from just 56% of the patient’s mother’s pancreas. The recipient needed small doses of insulin until 22 days post-transplant, which is not uncommon.
 - As of May 6, 2005, both the recipient and the donor were insulin-free. Responding to audience questions, Matsumoto confirmed that the recipient was C-peptide negative before the transplant; that the islets were not purified or exposed to cold ischemia before transplant; and that the Edmonton protocol for immunosuppression was initiated one week prior to the transplant (because the transplant was scheduled, the ideal situation of pre-transplant recipient preparation could be realized).
 - So why aren’t insulin-requiring diabetes patients queuing up for living related donor islet transplants? We know that since 1979, 150 living related pancreas transplants have been performed, accounting for less than 1% of all pancreas transplants. We believe the primary reason that living related donor pancreas transplant has remained rare is the same reason why living related donor islet cell transplantation is unlikely to take off: risks to the donor are *high*.
 - Usually the spleen is removed as well as part of the pancreas, entailing a very invasive surgery. Living pancreas donors (as well as the one living islet cell donor to date) face a much higher risk of developing type 2 diabetes if they become insulin resistant as they age. Many surgeons at both IPITA and AIDPIT (described below) were unenthusiastic about the prospect of causing a new case of diabetes in order to cure a pre-existing case.
 - Perhaps more compelling is that the best candidates for experimental living related donor islet transplantation are likely also candidates for established transplantation protocols

such as pancreas autograft – replacing someone’s pancreas with some of his or her own pancreas that was saved for later within the near term after pancreatitis diagnosis – or cadaveric pancreas transplantation (>20,000 performed to date).

- Patients with autoimmune diabetes (type 1 or LADA) are usually not high up on pancreas transplant waiting lists unless they are also waiting for a kidney as mortality rates for patients who need both a pancreas and a kidney are significantly worse than mortality rates for people waiting for a pancreas alone. At least in the West, neither living related pancreas nor living related islet donation offers much hope for those of us whose bodies are likely to react to – not only to reject – donated insulin-making cells. But for those whose diabetes is the result of incidental rather than autoimmune beta-cell destruction or dysfunction, living related pancreas or islet cell transplants may become an option, which would increase the number of cadaveric pancreata available for research and experimental transplantation.
 - Mark your calendars – next IPITA is in Chicago in 2007.
- **#5: IV International Assisi Symposium: New Technologies for Insulin Replacement: Artificial Pancreas and IT & Islet Transplantation – Assisi, Italy – April 28–May 1, 2005**

About 150 of today’s guiding lights in diabetes technology and islet transplantation gathered in the historical, gorgeous stone town of Assisi for this stellar workshop. The fourth Symposium meeting since 1981, this event offered attendees a crash course in the latest diabetes technology. While the Clinical Diabetes Technology meeting in San Francisco had emphasized the application of currently and potentially available therapies, this meeting revolved more around investigational devices and lessons to be learned from devices that have failed. Below we have selected some of the most interesting presentations that we heard there. The final program is unfortunately not available on-line (if you’d like a copy, e-mail info@closeconcerns.com). If you wondered whatever happened to the Pendra and GlucOnline, if you want to hear recent discussion on Medtronic’s closed-loop system, if you care about efforts to develop an artificial pancreas, read on

Pendra goes Dutch: lessons for the CE mark in Europe – Dr. J. H. De Vries

- History
 - 2000: Pendragon brought out the Pendra – three papers and 18 abstracts published
 - Advantages: noninvasive, glucose trending alarm, operation duration up to a few months
 - Pendra disadvantages: frequent calibration, 30% of patients had skin reactions to it
- May 12, 2003: CE mark achieved (“CE = C€,” Dr. De Vries said)
 - In Holland, purchase price was €1250 or €95/month for a two-year lease
- Clinical performance: Diabetologia 2005; 48 (6)
 - 35% correlation with SMBG (industry standard 90%)
 - 52% MAD (industry standard 11%)
 - On a Clarke Error Grid Analysis, 4.3% of failures fell in the E-zone, representing a meaningful risk of inappropriate treatment decisions
- Last year, a Dutch Pendra symposium was canceled two days before it was scheduled to occur
 - Two members of the Scientific Advisory Board resigned
 - The Dutch importer ended its relationship with Pendragon Medical
 - Pendra withdrawn from the market
 - Bankruptcy declared spring 2005
- Lessons for Europe

- Transparency of CE approval needs to be a priority because it is likely that CGM products will go to patients directly
 - MAD <25% seems like a good goal for CGM. (CC Note: We recall hearing, “*We need to do more research on that...*” in response to numerous audience questions at the Pendra symposium at the 2003 IDF/EASD meeting – a cautionary tale).

Continuous Glucose Monitoring: Key challenges to replacing episodic SMBG – Dr. S. Noujaim (Lifescan)

- o Recent Lifescan data on measured glucose lag was conveyed - yes, we thought this was interesting too!
 - Pressure on the alternative site from which a glucose reading was going to be obtained yielded remarkable results
 - Before lag mitigation with pressure, lag was 38.3 mins., SD 11.5
 - After lag mitigation with pressure, lag was 2.5 mins., SD 6.6

Joint microdialysis for continuous glucose monitoring – Dr. T. Vering (Roche)

- o Roche experience with SCGM
 - Excellent sampling efficiency, high glucose sensor stability, single calibration per 24h
 - >30,000 hours of patient use data collected, successful in trials lasting up to five days
- o Learnings
 - System characterized as robust and reliable, high recovery obtained, acceptable convenience is an important device attribute, integrated fluidics cause a complex system
 - A complex system is expensive; SCGM is best suited to be a reference system
- o Why have a reference system?
 - To explore the benefits of CGM, for comparison to SMBG, for comparison with other CGM devices, and to understand physiology better/improve therapy
- o Concept of Roche reference system
 - Microdialysis
 - Continuous flow sampling
 - Push-pull modes
 - *Ex vivo* determination of glucose
 - Flow sensor for system control
 - Parts: Disposable microdialysis catheter, pump, disposable flow through sensor, and disposable flow sensor
- o Conclusions
 - CGM is of “critical importance” (c.f., recent diagnostics call, page 28)
 - Microdialysis is best suited for use in a reference system
 - Clinical investigations will be helped by a reference system

Clinical experience with the Guardian Continuous Glucose Monitoring System and the Integrated Sensor/Pump Platform – Dr. John Mastrototaro (Medtronic MiniMed)

- o Medtronic MiniMed’s CGMS is useful for making therapy adjustments to improve outcomes
- o The Guardian is a wireless version of the CGMS
 - No real-time values are displayed but alarms are sounded for hypo- and hyperglycemia
 - Calibration must be performed once every 12 hours; studies are now being done using the Guardian RT
- o Guardian trial results
 - Hypoglycemia: When glucose measured ≤ 70 mg/dL by SMBG, Guardian had 85% sensitivity and 85% specificity, but one-third of events were missed when the hypoglycemia alarm was set at 70–75 mg/dL

- There is a sensitivity/specificity tradeoff: patients will decide whether they can take nuisance alerts
 - Hyperglycemia
 - Setting the alert at 250 mg/dL meant that Guardian missed 42% of high blood glucoses detected by SMBG. (The sensor under reads at high blood glucose levels: when the hyperglycemia alarm was set at 195 mg/dL, the sensor was said to be 91% sensitive.)
- o Regulatory status
 - Mastrototaro forecast FDA approval for Guardian RT in 2-3 months (CC Note – on its recent earnings call – more on that below – management confirmed “this summer”)
 - The device is already approved in Europe according to the company website
 - At the ADA, Medtronic will show early results from the European GuardControl study. Full GuardControl results will be available early in 2006.
- o Integrating Guardian RT into MDI will expand therapy options, it was said
- o Sensor-augmented pump will provide more data and the tools to use the data
 - Results of a one-year trial in 10 Medtronic MiniMed employees using the sensor-augmented pump
 - In 90 days, average A1C of 7.5% was reduced to 6.8%
 - Only one of the 10 participants was at goal before the trial; seven out of the 10 were at goal after 90 days, an impressive result assuming hypos were also minimized
 - This data will be coming out “in the future”
 - A clinical study is being started to look at 140 subjects aged 12 to 80
 - Some of the group will have six months on a sensor-augmented pump; some of the group will have six months on standard pump + SMBG
 - After six months, a six-month continuation will allow the standard group to switch to the sensor-augmented pump (this will keep them in the trial) and the original sensor-augmented pump group will be allowed to keep using the system
- o Questions
 - What is the distance range for communication between Guardian sensor and display device?
 - Dr. Mastrototaro: Communication can still take place even if sensor is 2 to 5 meters away from the device. However, if someone is sleeping on his/her stomach and has the Guardian sensor applied to his/her abdomen and the pump clipped on the back of his/her pajamas, the sensor is not able to communicate to the pump through the body
 - Dr. Mastrototaro said that trending information is being added to versions of the Guardian RT presently under development
 - Time frame for sensor-augmented pump to become available?
 - The strategy with regard to the FDA is to wait for the Guardian RT to be approved, then to return to the FDA to ask what studies will be required for the sensor-augmented pump approval. The best-case scenario is that the FDA would grant a real-time review. The most likely scenario is that the product would be approved within six months via PMA supplementary review. One year was thought to be the greatest amount of time between the submission and approval. Needless to say, the plan is for the sensor-augmented pump to be launched in Europe before the US

Closed loop implantable pump – Dr. Eric Renard

- o Even with implantable insulin pumps, we don't achieve normoglycemia
 - A closed loop system is necessary for stable normoglycemia
- o Why intraperitoneal insulin infusion?
 - Non-reliable reproducibility and delayed action of subcutaneous insulin make stability through subcutaneous insulin therapy hardly achievable in the long term

- Subcutaneous insulin therapy offers poor reactivity when insulin needs vary rapidly; intraperitoneal insulin delivery better mimics physiology but it is not exactly physiological
 - o Two methods of CIPII: Medtronic MiniMed implantable pump and Disetronic Dia-Port
 - Dia-Port adverse events: local events, catheter obstruction, infections
 - Insulin aggregation in implantable pumps can be handled in a 10-minute outpatient rinsing procedure
 - Implantable pumps require major surgery; Dia-Port is less major surgery
 - o Why do we need an IV glucose sensor?
 - Guardian subcutaneous sensor needs 3.9 to 5.0 calibrations per day. This is a big deal.
 - Subcutaneous sensor drift is problematic
 - Implanting a Medtronic MiniMed IV glucose sensor is a day surgery; the sensor is implanted in the vena cava to avoid thrombosis
 - Lapeyronie Hospital data on IV sensor: MAD 18.8; $r = 0.85566$; 95% of values in Zones A + B of the Clarke error grid (CC Note: This data looks very good. We would like to know how many of that combined total fell in Zone A [excellent accuracy] and how many from Zone B [decent accuracy])
 - o To achieve a closed-loop, algorithms need to be developed to cope with delayed insulin absorption and glucose excursions
 - o Where are we now?
 - Making a step towards an artificial beta cell
 - Intraperitoneal insulin has a lot of advantages and some problems
 - Glucose sensor is improvable in terms of invasiveness and delays, and a new generation product is being trialed soon
 - Effectiveness of PID needs refinement
 - o Discussion
 - Dr. Bill Tamborlane: Even a 200 mg/dL rise after a meal before return to baseline is better than the current situation. (Tamborlane referred to the CGMS study done at Yale in 2003 that found diabetic toddlers' glucose levels consistently in the 300 mg/dL range after meals – see Boland, et al. *Diabetes Care* 2001; 24: 1858-1862)
 - Dr. Kerstin Rebrin (Medtronic Minimed) pointed out that, according to the dates on his slides, Renard's data relating to the CGMS was generated in 2000. This means that the data referred to the first-generation CGMS, not to the CGMS Gold. We wonder what Renard's presentation would have looked like with CGMS Gold data, given that the Gold version offered major improvements compared to the original CGMS device.
- **#6: Diabetes UK – Glasgow, Scotland – April 20-22, 2005**

Attending Diabetes UK is a reality check: We see the UK as a nice place to visit (or live) but a bad place to live *with diabetes*. Topics for discussion in diabetes care are necessarily different in the context of socialized medicine: the bottom line, not the evidence base, frequently drives treatment decisions. We observed great interest in the science underlying advanced and emerging diabetes therapies among the clinicians present, but little enthusiasm for implementing new treatments due primarily to healthcare providers' anticipation of insufficient funding. The following are our observations from the stimulating sessions on cardiovascular disease, the socioeconomic burden of diabetes, recent and forthcoming advances in diabetes treatment, and diabetic metabolism and physiology. We selected these sessions because they offer insight into hot topics in clinical diabetes care in the UK that might also have implications for other markets. The complete conference schedule may be downloaded from <http://www.diabetes.org.uk/apc/apc2005/programme.htm>

Joint Symposium with Heart UK: Lipids in Diabetes: background, management and cardiovascular prevention – Drs. Chris Packard, John Chapman, and Tony Wierzbicki

Highlights from the panel discussion and audience questions:

- What about young type 1s? Would you put all type 1s on a statin from diagnosis?
 - It may be that high peripheral insulin levels make it hard to use the results of cholesterol tests to gauge CVD risk
 - We might find attenuated HDL cardiac protection despite high HDL levels
 - The Heart Protection Study, highlighted within this symposium, included 6000 patients, of whom 11% had type 1 diabetes. Results showed that patients with type 1 did far better if they took a statin, even if they had no formal diagnosis of heart disease (*The Lancet* 2003; 361: 2005-2016)
- Many of us are assured by high HDL in type 1 diabetes: Should type 1s with no microvascular disease be on statins? Are the LDL: HDL ratios irrelevant in type 1 diabetes?
 - We need to develop markers to determine whether HDL is protective in type 1
- Should we get rid of milk, move to a Mediterranean diet, and drop hydrogenated fat from foods?
 - Possibly – the sort of diet that is now common in the UK has been common only since the Victorian era, and it doesn't seem to have done the nation any good.
- Should all patients with any form of glucose intolerance be on a statin?
 - The panel claimed not to suggest that *every* patient with IGT ought to be on a statin (but, they seemed to imply, many might do better on a statin than they would do without one)

Oral abstracts – Metabolism

- Data from the Three Amigos studies on Amylin's exenatide were presented in three abstracts.
- More than half the audience made for the exits immediately after the exenatide presentations!
 - This was interesting to see as UK thought-leaders in diabetes have expressed skepticism about whether incretin hormone-based therapies for type 2 will be widely utilized in the UK. We assume that the audience hadn't seen much of this data, although it had been released previously in the US.

PYY and ghrelin: opposing forces in meal-to-meal appetite regulation – Dr. Simon Aylwin

- Insulin has a modulating effect with leptin
- The GI tract regulates appetite between meals; the vagus nerve communicates to the brain
- NPY and AGRP system: orexigenic (appetite-increasing)/anabolic (building up the body)
- PJMC system: anorexigenic (appetite-reducing)/catabolic (reducing the body)
- Melanocortin pathway ensures that if you knock out any of several genes, you get a very obese mouse. The melanocortin pathway is heavily implicated in energy homeostasis and weight maintenance in humans too.
- Ghrelin was discovered in 1976
 - Reverse pharmacology; the name comes from the fact that it is a stimulant of growth hormone
- Chronic ghrelin administration in rats caused sustained food intake and weight gain
 - Ghrelin and insulin have a mutual antagonism
- Lean humans ate 30% more at a buffet after a ghrelin injection compared to subjects who did not have the injection, but ghrelin is not a cause of obesity
 - Excess ghrelin is seen in Prader-Willi syndrome, anorexia, cancer cachexia, heart or renal failure
- Low ghrelin is commonly observed in obesity
- PYY was discovered in 1995
 - Batterham, *Nature* (2002): PYY inhibits food intake up to 30%

- Obese subjects are not immune to PYY, despite being immune to leptin
- PYY is restored after bariatric surgery
- Roux-en-Y gastric bypass causes a change in PYY (*Endo* [2004])
- Borg, Le Roux, Aylwin (2004): six months post-surgery, Roux-en-Y results in even more PYY production and increased GLP-1, as well as greater postprandial insulin levels
- From our perspective, this session offered insight into the science behind human body weight regulation. As we see potential therapies for obesity turn into realities, we'll need to keep in mind the complexity of human metabolism.

Global burden of diabetes mortality – Dr. Gojka Roglic (WHO)

- Between three and five percent of the WHO budget goes to non-communicable diseases
 - Most donations to the WHO are for AIDS, malaria, TB, etc.
 - Only 0.1% of international aid goes to non-communicable diseases
 - Only 2.5% of World Bank loans are made for health and nutrition
- Diabetes accounts for 1.5% of total mortality per year, according to world health reports
 - Roglic thinks this statistic is too low because it does not include IGT; plus, death registration data is useless as only one-third of the world has reliable death registration
- DISMOD II: tool for ascertaining disease prevalence, downloadable from WHO website
 - Several journal articles were used to construct it
 - Roglic's figures based on DISMOD II data: globally, 2.9 million deaths per year due to diabetes, which would account for 5.2% of mortality, on a par with HIV/AIDS
 - Worldwide percentages of deaths among 50–59 year-olds due to diabetes
 - Western Europe: 10%; Africa: 10%; Asia: 10%; Eastern Europe: 12%;
 - USA/Canada: 20%; Latin America: 20% (higher among females)
 - Diabetes is the sixth leading cause of death in the world; in the US and Canada, diabetes should be considered the third leading cause of death. Most estimates rank diabetes as the sixth leading cause of death in the US because deaths due to cardiovascular disease (CVD) in the presence of diabetes are likely to be recorded as CVD deaths even if diabetes was the underlying cause of the CVD.
 - (CC Note: It's disconcerting that mortality rates associated with diabetes are higher in the US. It seems Americans have greater predisposition to diabetes in the presence of obesity [for a variety of reasons, possibly linked to our heterogeneous genetic heritage] *and* diabetes is managed less well in America than it is in Europe: the average A1C of the US is ~9.3%; in Europe it's lower, according to Dr. Satish Garg, among others – not good, as we understand it, but less bad. We suspect this is because more type 2 patients take insulin there (and probably earlier, though they also have the same problems about patient and HCP resistance there).

Hot topic: New Therapies/Pumps – Drs. Cliff Bailey and David Kerr

Dr. Cliff Bailey

- New therapies or type 2 diabetes:
 - Fixed-dose combinations reduce the number of pills required per day, possibly increasing adherence to therapy
 - Glucovance and metaglip (not available in Europe yet)
 - Avandamet
 - Avandaryl-RS – coming soon
 - Fortamet – two years or so away
 - Metformin + “you-name-it” – probably on the way
 - Statins, aspirin, antihypertensives (ARBs, ACE-inhibitors, CCBs), oral antidiabetic agents could be combined with metformin

- Bailey joked that metformin could even be combined with Viagra or Prozac
- GLP-1
 - Exenatide – see Fineman, et al., *Diabetes* (2002)
 - Big question: β -cell preservation/proliferation?
 - Big problem with natural GLP-1 is that it is quickly degraded by DPP-IV. GLP-1 analogs, incretin mimetics, and DPP-IV inhibitors are strategies for subverting this process
 - LAF237 (Vildagliptin), a DPP-IV inhibitor that allows for better utilization of endogenous GLP-1, showed a 1% reduction in A1C, maintained over one year
- Symlin (pramlintide), Amylin's amylin analog, increases satiety, reduces postprandial hyperglycemia, causes moderate weight loss in type 1s
- TZDs are available
 - Non-TZD dual PPAR-agonists in development: muraglitazar (BMS/Merck), tesaglitazar ("Galida" – AstraZeneca)
- Endocannabinoid receptor blockers will apply in patients with increased waist circumference and smokers
- CC Note: The session that followed was not as crowded as we would have liked to see. It conflicted with the tea break – to boot, at present, many UK clinicians face government-imposed budgetary limitations that dampen their enthusiasm for pump therapy.

Dr. David Kerr

- CSII (insulin infusion pump) vs. MDI (multiple daily injection)
 - Quantitative data not great (there just isn't a lot available) – qualitative data shows patient preference for CSII. (CC Note: WE note that historically there has not been as much pressure in the US for medical devices to show data from randomized controlled trials, etc., but we believe this is changing, to due payor pressure.)
 - Children do better on pumps, according to a recent *Diabetes Care* (2004) study
 - We personally feel *strongly* that even if A1C isn't always so different in studies, glycemic variability is less – or would be less, if it were measured, which is typically has not been. Hope we will see this start to change ...
 - Indications for a pump: frequent hypoglycemia, dawn phenomenon, complications, pregnancy, patient choice, quality of life (CC Note: Kerr is one of a select few UK clinicians actively lobbying for pregnancy, patient choice, and quality of life to be added to the official National Institute of Clinical Excellence criteria for pump therapy.)
 - *Diabetologia* 2004: using an insulin analog in a pump reduces A1C by 0.2%
- Dia-Port: Dr. Kerr is running a study in which four patients have received Dia-Ports (CC Note: Dia-Port is a surgically implanted catheter for intraperitoneal insulin infusion with an external insulin pump. It was a Disetronic product and Roche now distributes it in Europe only)
 - Indications: failure of MDI/CSII; trouble with injection/infusion sites
 - Problems/risks: post-operative hematoma, staph, increased insulin needs
 - Results: better glycemic stability, less hypoglycemia, less retinopathy
- Dr. Kerr will show some data from the GuardControl trial (Medtronic MiniMed) at ADA
 - GuardControl is a 162-patient, Phase IV, randomized, controlled, multi-center, clinical study to assess whether type 1 diabetic patients in poor control can improve using the real-time values of Guardian RT vs. conventional SMBG. Sites in Berlin, Paris, Israel, Milan, Slovenia, Sweden, and the UK (CC Note: Kerr's base, Bournemouth, is the UK site. <http://www.clinicaltrials.gov/ct/show/NCT00111228> for inclusion/exclusion criteria, primary and secondary endpoints, contact details, etc.)

- Miniaturized insulin pumps
 - Starbridge Systems (Wales) has in development a three-day use, wireless, low-cost (~US \$6-24/ea.); will provide basal insulin for type 2 patients. Dr. Kerr mentioned that he is about to try the system in a patient
 - Insulet OmniPod (Kerr showed a picture but did not describe the product in detail)
- Conclusions
 - Indications for insulin pump therapy are increasing
 - We need to do more work on quality-of-life issues
 - We should move patients on MDI to insulin analogs
 - We should use insulin analogs in pumps
 - We should have more specialist centers (in the UK) to oversee pump therapy
 - Small is beautiful: miniaturization is the future

Proinsulin C-peptide: New physiological findings and therapeutic possibilities – Dr. John Wahren

- Diabetic polyneuropathy (DPN) occurs in approximately 100% of type 1 diabetes patients by 25 years after diagnosis
- In type 1s, neuropathy progresses more rapidly and more severely than in type 2s
 - Progressive/nodal degenerative
- Only 35% of type 2s have neuropathy 25 years after diagnosis
 - Slow progression/no nodal changes
 - CC Note: We are not convinced that these data should be relied upon. Today, even brand-new 25-year data on type 1s relies on at least 10 years of pre-DCCT-style conventional diabetes management. Whether post-DCCT-style intensive management can reduce DPN by 25 years after diagnosis has yet to be shown but we're assuming that use of better insulins and management tools [monitors and pumps] would improve long-term outcomes, were they to be tested. More on that point in the year 2020 or so. Really, we'd love to see another DCCT done today, with new insulins, new pumps, new monitors, new focus on reducing glycemic variability, etc. We understand the cost is mind numbing – well over \$150 million probably – but aren't costs associated with complications pretty astronomical? This seems like something that government and industry would both do well to pay for, given potential findings. Yes, we know this is a naïve statement (right, right, whose pumps would be used, whose monitors, etc.). That doesn't mean it isn't true, in our view.
 - CC Note the Second: Considering the mortality data, historically many type 2 patients have not survived 25 years after diagnosis¹. Perhaps those who do survive for 25 years have some degree of genetic protection from complications?

¹ **Distribution of Duration of Diabetes Among Adults Aged 18 – 79 Years, United States, 2003**

<http://www.cdc.gov/diabetes/statistics/duration/fig1.htm>

Years Diagnosed	Percent
0-4	38.2
5-9	21.5
10-14	14.3
15-19	8.4
20-24	5.7
25-29	3.7
30+	8.2

So this shows that in 2003, less than 12% of adults with diabetes had had it for more than 25 years, suggesting that it is hard to find people with diabetes who have been diagnosed for more than 25 years. Too, this suggests that as diabetes has been documented as a disease for over 2000 years, almost 90% of people with diabetes die before they've had it 25 years. Our own fine print would point out that many are diagnosed long after they have actually had the disease and that today,

- Hypothesis: neuropathy in type 1s arises from lack of C-peptide, while in type 2s it arises from hyperglycemia
- Conclusion
 - C-peptide ameliorates functional/structural changes to peripheral nerves
 - C-peptide replacement for 3-6 months in patients with early-stage DPN improves sensory nerve function
- Question: Could we be seeing more DPN because newer insulins do not contain C-peptide the way that old insulins (pre-1980s) did? Answer by Wahren: No. Even if old insulins did contain C-peptide, it would have been porcine C-peptide and the binding wouldn't be the same as human C-peptide.
- **Insulin secretion action: a physiological conundrum – Dr. David Matthews (Oxford)**
 - Insulin secretion/action affects the liver, muscle, fat cells, brain, and so on
 - Insulin is not just about blood sugar
 - Insulin signaling reaches multiple organs with just one signal
 - Order of magnitude is a huge issue – type 2s typically have far too little insulin
 - Insulin dosages range from four to 400 units in clinical practice. This is two orders of magnitude – this is huge; no wonder primary care healthcare providers are distressed by prescribing insulin
 - Problem of multiplicity: 2000m cells in the body and all are signaling insulin
 - Insulin resistance is reciprocal of insulin sensitivity
 - It is unlikely that all insulin resistance is a defect – physiological change is not pathological: *difference ≠ defect*
 - But what is *normal*?
 - Stimulants of β-cell: glucose, leucine, NEFA, arginine
 - Insulin will then do any number of things
 - Insulin action is concentration-dependent and time-dependent, by tissue type
 - HOMA data: as one grows obese, insulin secretion rises, compensating for insulin resistance
 - We know that insulin is pulsatile, depending on concentration, time, feedback
 - But how do billions of cells *cope*? Every cell makes its own decision. According to Matthews, there is a “bizarre democracy of cells” based on the problem that the signal is imprecise; Matthews calls this a “delegated physiology”
 - Problem of a diminishing target: if you flood cells with some substance, they become insensitive to it (downregulation), but the signal site is different around the body
 - Polonsky: obese non-diabetic and normals have the same degree of regulation/pulsatility even if concentrations of insulin are different
 - Glitazones
 - Pioglitazone: see Wallace and Matthews, *Diabetic Medicine* 19 (2002): we can start to think of insulin resistance as physiological rather than pathological
 - AM vs. FM radio frequencies illustrate situation of clear signals vs. fuzzy signals within body
 - AM: cheap, big signal, easy to decode, noisy, requires retuning
 - FM: expensive, small signal, hard to decode, clear, can be pre-set
 - The endocrine system is like AM radio; the nervous system is like FM
 - Conclusions
 - Insulin resistance is not a defect – we'd be dead without it
 - It is a direct result of a crude/cheap signal
 - Upregulation and downregulation act on insulin signaling
 - Insulin resistance is generally physiological

insulin, drugs, and treatment modalities have improved greatly – so things might not be as bad as they look. However, they look pretty darn bad. Much MUCH room for improvement clearly exists.

- **#7: Clinical Diabetes Technology – San Francisco, CA – April 15-16, 2005**
 How could we not take advantage of two marvelous days of diabetes technology in our hometown?! Many readers are already familiar with the Diabetes Technology Society meeting that Dr. David Klonoff organizes each November (also happening in SF this year, Nov. 10-12– see <http://www.diabetestechology.org>). The recent Clinical Diabetes Technology meeting is a superb outgrowth of that conference, in terms of learning and gathering. The first day focused on clinical continuous glucose monitoring; the second was devoted to insulin delivery strategies. The complete program for both days is available on <http://www.clinicaldiabetestechology.org>.
 - **Real-Time CGM Technology – Ready, Get Set – Dr. David Klonoff**
 - Three phases of blood glucose monitoring
 - Most of the 20th century: Urine
 - For the past 20 years: SMBG
 - The 21st century: continuous glucose monitoring (CGM)
 - Klonoff recently found 868 articles on CGM on PubMed
 - Analogies: SMBG is like a camera and CGMS is like a security camera; a still shot does not tell you nearly as much as a video, even if the video resolution is not perfect. One SMBG reading is not appropriately contextualized, even if it is near laboratory accuracy
 - There is a sensitivity/specificity trade-off, at least at present
 - Target patient characteristics for CGM are nearly the same as for CSII (that is, general enough to ensure a wide audience, but not totally vague): Intelligence, mechanical dexterity, reliability, and diabetes knowledge
 - Industry and clinicians can work together to improve patient care
 - Industry can develop better technology; performance standards
 - Clinicians can improve education and outcomes trial data
 - **A New Look at Error Grid and Continuous Glucose Error Grid Analysis – Dr. William Clarke**
 - The original error grid was developed for point accuracy
 - There was no rate of change or trending data implicated in its development; it won't work for CGM
 - Continuous Glucose Error Grid Analysis (CG-EGA) puts data into new ranges of accuracy
 - Some data points become more accurate, some less so, when the data is transferred from a traditional error grid to a CG-EGA
 - Using the rate error grid: if the rate is incorrect, then we may treat inappropriately
 - Rate change grid tracks whether the CGM device is accurately reflecting a trend
 - Using CG-EGA, the Freestyle Navigator moves to 75% in the CG-EGA A zone and 98.7% accuracy overall, vs. 68% accuracy according to the old EGA
 - Rate change grid: Navigator has 92.2% accuracy
 - 70.9% accuracy at <70 mg/dL
 - 93.9% accuracy at 70-180 mg/dL
 - 89.1% accuracy at >180 mg/dL
 - Outstanding issues
 - How do we convert the data so that it is clinically meaningful?
 - How do we train patients/clinic to use/interpret/use CGMS?
 - Do we measure A1C improvement? Reduced glycemc excursions? Ideal outcome detection methods not obvious at present

- o **Glycemic Variability – It’s Not Just About the A1C Anymore – Dr. Irl Hirsch**
 - Maybe we have misinterpreted the results of the DCCT
 - Perhaps the point is that reducing glycemic variability, not absolute A1C, will prevent/delay complications. (Thought leader Dr. David Nathan suggested this in 1995)
 - PKC- β activation leads to microvascular damage; Ruboxistaurin (being developed by Lilly) and mannitol are effective inhibitors of PKC- β
 - Glycemic variability appears to have significant effects on the kidneys as well; diabetes care standards-setters should not look only at the A1C as preventative re complications, but also at glycemic variability
 - The higher the standard deviation, the greater the oxidative stress; Hirsch discussed briefly the glycemic variability index to reflect both A1C and SD - we look very forward to hearing more – and we know we will be. In terms of actionable learning that can improve care *today*, we believe this was best presentation of the conference (happily, there was *much* great competition) – now let’s just hope it happens.

- o **Incretin Therapy: What’s Coming This Year – Dr. Steve Edelman**
 - Advances since 1995 include seven new oral drugs, fast-acting insulin analogs, better insulin pumps and pens, faster meters, and diabetes management software programs
 - Despite these innovations, 63% of diabetes patients are not meeting A1C targets (Koro, et al., *Diabetes Care* 2004; 27: 17-20)
 - An incretin hormone stimulates more insulin to be secreted when glucose is delivered orally vs. IV
 - Effects of GLP-1 infusion in type 2s
 - Acute: enhanced glucose-dependent insulin secretion
 - Sub-acute: transcription of pro-insulin and biosynthesis of insulin
 - Chronic
 - Decreases beta-cell apoptosis
 - Increases beta-cell neogenesis, proliferation, and hypertrophy
 - Edelman: “If you give this drug early enough, you may prevent type 2 diabetes.”
 - Edelman showed several slides illustrating data from Zander, et al. *Lancet* 2002; 359:824-830
 - *Very* good data here – check this article out! (CC Note: See entire piece at *The Lancet* [\$30 charge, a good deal for this data] or read the abstract free at <http://tinyurl.com/csq>)
 - Ways to enhance GLP-1 action
 - GLP-1 chronic infusion (actual GLP-1 has such a short half-life that it needs to be infused for it to be effective)
 - NVP LAF237 (Vildagliptin)
 - Novo Nordisk’s Liraglutide
 - Amylin’s Exendin-4/exenatide
 - Edelman showed data about the effects of Exendin-4 + metformin, Exendin-4 + sulfonylurea, and Exendin-4 + sulfonylurea + metformin in type 2s (3 Amigos). See Poon, et al., *Endocr Pract* 2004; 10 (Suppl. 1)
 - At the ADA, Edelman will show data about the use of Symmlin in *non-diabetic* obese subjects
 - “Impressive weight loss” and the patients were said to have no problems with the injection regimen
 - Liraglutide controls weight better than insulin (Nauck, et al., *Diabetes* 2004; 52 (Suppl. 2, A83)

- Liraglutide takers do not lose weight because of gastric problems – weight loss resulted from another mechanism
 - Liraglutide does not suppress glucagon during hypoglycemia: it's a “smart hormone”
 - Liraglutide inhibits apoptosis in Zucker diabetic fatty rats
 - Chang, et al., *Diabetes* 2003: even one dose of Liraglutide can restore insulin sensitivity
 - Downside; constipation *might* be a side-effect of Liraglutide
 - Novartis's DPP-IV inhibitor: LAF 237 (Vildagliptin)
 - Binds competitively and specifically
 - Once a day *oral* administration
 - 24-hour dose duration
 - Ahren, et al., *J Clin Endocr Metab* 2004: Vildagliptin study
 - Combined with metformin
 - Lower A1Cs maintained for over 1 year
 - No weight loss, no weight gain, no gastric side effects
 - Conclusion: There is much excitement about “other hormones:” leptin, PYY, adiponectin, amylin, ghrelin, GLP-1
- o Update on Inhaled Insulin – Dr. Jay Skyler**
- Lungs have a tennis-court sized absorptive area
 - But pulmonary insulin delivery is not easy: insulin bioavailability is 10-15%
 - 15-30% inpatient variability, equal subcutaneously injected human regular insulin
 - Pulmonary insulin delivery was first proposed in 1925. It has resurfaced every decade since
 - Current products in development addressed by Skyler include:
 - Pfizer/Aventis/Nektar Exubera: dry powder insulin; mechanical inhaler. Exubera filed for FDA approval March 2. UK approval is expected first, which surprised us because the National Health Service tends not to pay for new technology (CC note: <3% of type 1s in the UK have insulin pumps, compared to about 10% of type 1s in Germany and 15-20% of type 1s in the US)
 - Novo Nordisk/Aradigm (now totally under Novo Nordisk's auspices): electronic inhaler. One can measure the amount to be delivered very precisely...whether all is absorbed is another issue; now in Phase III.
 - Mannkind: dry powder insulin Technosphere; mechanical inhaler – very rapid insulin absorption suggested. First phase insulin response could be major advantage.
 - Lilly/Alkermes: dry powder insulin; breath-activated inhaler – MIT developed the technology; now in Phase II. Lilly/Alkermes's formulation acts more rapidly but lasts longer than injected subcutaneous lispro
 - Kos: liquid, multi-dose insulin; breath-activated inhaler – has a dose counter to measure breaths; now in Phase II
 - BMS/QDose: dry powder insulin; breath-activated inhaler
 - Aerogen: liquid insulin formulation; battery-assisted, breath-activated inhaler; suspended
 - Dura “Spiros”: dry powder insulin; suspended
 - AstraZeneca: dry powder insulin/absorption enhancer; dropped from pipeline
 - Coremed Alveair: only pre-clinical abstracts to date
 - Generex: dry powder formulation; buccal, not pulmonary delivery
 - A 2001 paper showed that the action of pulmonary insulin is dose-dependent (Brunner et al. *Diabetologia* 2001; 44: 305-08)
 - Exubera and subcutaneous lispro have very similar onset of action but Exubera wears off more slowly than subcutaneous lispro

- Smoking makes pulmonary insulin work better; however, during upper respiratory infections the glucose decline is blunted
 - Skyler, et al., *Diabetes Care* 2005 (in press): subcutaneous insulin compared to inhaled
 - Subcutaneous protocol: twice daily NPH + twice daily Regular
 - Subcutaneous group gained more weight than inhaled group
 - AeRx system Phase II data (Hermansen, et al., *Diabetes Care* 2004) suggests that inhaled insulin may in lower fasting plasma glucose levels
 - Prandial Kos insulin was similar compared to Lantus in type 2 patients in a 12-week unpublished study – both Lantus and Kos inhaled insulin caused a little weight loss, which was surprising
 - Phase III Exubera
 - Good results when combined with oral agents
 - Tony Barnett (Birmingham, UK) showed a 2.0 to 2.5% drop in A1C with the addition of Exubera compared to no change in oral therapy – we’re sure the baseline A1C had to be pretty high
 - Skyler’s own study showed not much change in A1C but the required dose increased a little over time
 - Safety and cost continue to be major questions.
 - The discussion of antibodies was of great interest. Skyler said pulmonary function is not influenced by antibodies, which are IgG, the ones usually associated with exogenous insulin therapy
 - The levels are just a fraction of what we used to see before 1972, when insulins were usually 8% “other” non-insulin matter/92% insulin
 - Conclusions
 - Inhaled insulin can be used for prandial insulin
 - Safety criteria met
 - Products should be approved by the FDA
 - Outstanding issues
 - Not a lot of improvement seen in populations already on insulin therapy before the initiation of inhaled insulin
 - Hypoglycemia is still an issue
 - Quality of life – studies show preference of inhaled insulin versus subcutaneous
 - Cost-benefit: inhaled insulin is very expensive
 - We need long-term safety studies
 - There is currently no data on inhaled insulin use in pediatric populations
 - Does cardiovascular exercise change the pulmonary absorption of insulin?
- **#8: American Heart Association Research Roundtable Luncheon – Palo Alto, CA – April 14, 2005**

This AHA luncheon featured a sobering talk by Dr. Steven Blair, President and CEO of the Cooper Institute in Dallas. His data on obesity underscored the magnitude of the crisis facing America and made us a bit anxious about the dessert served toward the end of the meal. We found Blair’s perspective a bit unconventional and highly intriguing,

o **A New Way of Thinking about Weight Gain**

- Why are Americans obese? Blair theorized that energy intake has remained constant while output has decreased. He acknowledged that the obesity epidemic may be the product of both an increase in consumption and a decrease in activity, but no one knows the extent to which each factor has driven obesity.
- Graphs of caloric intake for men over the past three decades show an increase between the late 1970s and the early 1990s, but this increase may be attributable in part or in

whole to a shift in survey methodology. So, the rise in average calories may reflect a more thorough system of data collection – now capturing the cream and sugar in the coffee, the butter on the baked potato – rather than a true upswing in consumption.

- A recent study explored the association between sitting and obesity, assessing energy expenditure and posture in two groups of people – a lean group including people with a BMI of 23, and an obese group with people with a BMI of 33. As one might expect, the heavier group sat considerably more, burning fewer calories – 364 calories fewer per day. We would note that their weight likely influenced their degree of activity as well as their lack of activity exacerbating their obesity, but the findings substantiate the intuitive importance of activity in weight trends.
 - **For us, the most interesting** aspect of Blair’s view on activity was his distinction between cardiovascular health and weight. A 1999 study found that fit people had half the death rate of unfit people *within each weight category*. That is, lean, fit people have half the death rate of lean but unfit people, and heavy, fit people have half the death rate of heavy but unfit people. Comparing across groups revealed that an overweight, active person may be in better health than a thin, inactive person. So, weight management aside, physical activity and fitness are crucial for longevity. We first heard this fit versus fat argument at the Canadian Diabetes Association meeting in 2003 and there, as here, it was found controversial but very interesting.
 - In studies considering a variety of risk factors and mortality in men, mortality varied by cardiovascular fitness, independent of smoking status, blood pressure, and cholesterol. Fit people who had significant risk factors for cardiovascular disease were much better off than those with medium or poor fitness and all of the risk factors.
 - Blair proposed that we need to think about “reengineering daily life to be less sedentary” to combat “the toxic environment” that breeds inactivity and obesity. This includes taking the stairs rather than the elevator, nixing the remote control, doing our own yard work and house cleaning.
 - More research is needed on the question of energy balance, but Blair’s theories about the role of inactivity in obesity suggests that promoting activity may be as critical as limiting intake in tackling America’s obesity epidemic.
 - We love the argument but know that 10,000 steps a day isn’t prescribed and followed by everyone, no matter how clear the benefits. It takes more than prescription – more time for exercise at school, safer walking paths, more funds set aside for safe and clean parks to exercise, etc. The list goes on. Still, the education was key, and we just have to get more of this out! One positive - we *do* think less dessert probably was eaten that afternoon. Is it a trend? Only time will tell. It’s like what we say about hyperglycemia – if it only hurt, we suspect we’d (the royal we, the patient with diabetes) would be in *so* much better condition overall.
 - Thank you to the VCs who gave us seats at their table!
- **#9: “New Frontiers in Monitoring: Brave New World – *But* – What to Do with the Data?” – Boston, MA – March 19, 2005**
 - A Diabetes Expo debate between Drs. Howard Wolpert and David Nathan**
 - The advent of continuous glucose monitoring (CGM) has raised many questions about how it will be integrated into clinical practice. The Boston Diabetes Expo in March featured a one-hour debate about the usefulness of CGM between Dr. Howard Wolpert of the Joslin Diabetes Center and Dr. David Nathan of the Massachusetts General Hospital. While CGM has been eagerly awaited by healthcare providers and patients, the debate suggested that it faces logistical barriers to immediate widespread uptake. The debate centered on the questions of whether and how healthcare providers can use CGM data effectively.

- Responding to the optimism surrounding CGM, Dr. Nathan criticized the current technology on a number of counts. He argued that healthcare providers will be overwhelmed with information that may not be accurate, unable to use it to benefit the patient, and that they will not be compensated for the extra time spent dealing with CGM data. Apart from healthcare provider use, he raised serious questions concerning CGM's usefulness to patients in four areas:
 - **Accuracy:** Nathan pointed out that current CGM systems have low sensitivity and specificity, particularly in the hypoglycemic range. The current specificity and sensitivity is too low for CGM to be safely incorporated in a closed-loop system.
 - **Practicality:** Although most envision a glucose reading being immediately available to the patient in real time, the present generation of the Medtronic MiniMed CGMS Gold yields data only at download, in the healthcare provider's office, and thus patients must do both episodic and continuous monitoring. Even with the Cygnus GlucoWatch G2 Biographer, episodic monitoring must be continued for purposes of calibration. Additionally, patients wearing an insulin pump now have to wear a pump *and* the CGM system, burdening the patient with multiple devices. Most importantly, present CGM technology does not eliminate the need for self-monitoring.
 - **Invasiveness:** Dr. Nathan had sharp questions regarding the CGMS and GlucoWatch technologies. He characterized the GlucoWatch as a "small electric chair," referring to the use of electric current to draw interstitial fluid through the skin. Minimed's CGMS requires a subcutaneous sensor to be inserted in the abdomen, similarly to the insertion of an insulin pump infusion set.
 - **Cost-effectiveness:** CGM has been estimated at \$51,000 per quality-adjusted life year (QALY)², compared with the approximately \$20,000 per QALY for the kind of intensive therapy used in the Diabetes Control and Complications Trial (DCCT). Dr. Nathan argued that the technology may currently not be worth the investment.

Dr. Nathan especially emphasized the dearth of controlled trials on CGM. While most speculators expect the technology to reduce episodes of hypoglycemia and to improve glycemic control, no randomized controlled studies have shown that the current technology has the potential to achieve these goals. One small study showed that more hypoglycemic readings were detected with CGMS, but critics of the study suggested that those may have been false readings. A larger study gave a rate of true positives of 25% and a rate of false positives of 15%, indicating both low sensitivity and low specificity. The largest study to date, sponsored by the NIH-supported Diabetes Research in Children Network (DirecNet), showed no difference in symptomatic hypoglycemia between type 1 patients performing SMBG and type 1 patients using both CGM and SMBG. Severe hypoglycemia was three times as likely in the GlucoWatch-wearing group, a phenomenon Dr. Nathan proposed might be related to patients over-correcting with insulin for high readings on the GlucoWatch. Reacting to elevated post-prandial glucose levels before a short- or rapid-acting insulin has peaked, might result in over-dosing through "stacking" boluses.

Studies conducted to date also suggest issues potential problems with patient compliance. Patients in the GlucoWatch study were able to use up to three disposable sensors per week, but most used only two, and this number decreased as the study continued. Patients experienced skin irritation and burns from the sensor. The GlucoWatch also did not appear to reduce hemoglobin A1C in the

² See superb NEHI report that we wrote about last month for further information on the \$51,000 figure and QALY more broadly (www.nehi.net).

study. Overall, Dr. Nathan argued that CGM is still inaccurate in the hypoglycemic range and difficult to use, and that it does not reduce hypoglycemia or yield lower A1Cs.

Dr. Wolpert defended CGM, emphasizing that it is a new technology in the early stages of development. He cited the development of the first home blood glucose meters in the 1970s, which were relatively inaccurate, cumbersome and difficult to use. Despite initial problems, they opened the door for intensive management and the development of intensive diabetes self-management as utilized in the DCCT protocol. Responding to Dr. Nathan's concerns about the lack of evidence that CGM lowers A1Cs and reduces hypoglycemia, Dr. Wolpert suggested that controlled studies will take place in coming years, when accuracy, reliability and ease of use of devices have been improved, and that it is far too early to dismiss the technology.

Dr. Wolpert made several points about the integration of CGM into clinical practice, drawing on his experience using CGM in a clinical setting at the Joslin Diabetes Center:

- **Healthcare provider use:** Joslin Diabetes Center has developed a program for patients to use the Medtronic MiniMed CGMS Gold, and Dr. Wolpert argued that the data has been clinically relevant. It has not overwhelmed healthcare providers, and they have created a system for digesting and applying the information.
- **Hypoglycemia:** In the follow-up study from the DCCT, the two conventionally and intensively managed groups' A1Cs equalized. The reasons for this lapse of the tightly controlled patients are not documented, but in a survey following the DCCT, 75% of patients cited fear of hypoglycemia as an impediment to tight control. CGM has the potential to address this problem.
- **Accuracy:** Again, the first generation of home blood glucose meters needed to be improved too. Researchers are working on the accuracy problems with CGM, including some promising research with membranes to reduce foreign body reactions to sensors. Additionally, CGM's ability to measure the rates of change in blood glucose can be incorporated into an alarm to warn patients of impending hypoglycemia, even if the point accuracy of these devices in the hypoglycemia range does not measure up to that of fingerstick monitors
- **Limitations of Episodic Testing:** Dr. Wolpert presented multiple case studies of instances in which relying on episodic testing would result in *incorrect* insulin dosing. Understanding the trend of blood glucose, rather than the blood glucose level at a specific point in time, is critical in making clinical judgments. Four daily glucose checks conceal many peaks and lows in blood glucose.
- **Behavior Modification Tool:** As part of the Joslin CGM program, patients are served lunch between training sessions. The lunch includes a high-glycemic index chocolate chip cookie. Dr. Wolpert suggested that the visible glucose spike in the CGM readings allows patients to understand better the consequences of their food choices.
- **Cost:** Dr. Wolpert did not feel that \$51,000 per quality-adjusted life year was too high a cost, and he noted that it would be important to show significant clinical improvements to encourage insurance companies to pay for the new technology.

Dr. Wolpert presented a strong case for the usefulness of CGM, and he demonstrated that a group of doctors have successfully integrated CGM data into their practice. In response to Dr. Nathan's concerns, he advocated for more patience with the technology, noting that the potential benefits are far too great to reject the first generation models, despite their limitations. Dr. Wolpert and Dr. Nathan agreed that glucose monitoring and control are essential to diabetes management, citing the DCCT and the dramatic reduction in complications that can result from good glucose control. Dr. Wolpert argued for CGM as a bridge to a closed-loop system, and both doctors agreed that this is an important goal for diabetes technology. Although Dr. Nathan identified a

number of obstacles for the new technology, Dr. Wolpert convincingly demonstrated that it has the potential to transform clinical management of diabetes.

Discussion highlights

Audience question: Why do patients have to do both episodic and continuous monitoring?

- Wolpert: The device is generating a current. Sensor drift occurs. The fingerstick is used to calibrate the device several times a day. Accuracy improves with increased calibrations. Newer technologies are developing ways of using external glucose solutions for device calibration
- Nathan: It doesn't seem likely in the near future that there's a way to get away from needing frequent calibration.

Audience question: What is the chance of realizing an integrated pump and sensor in terms of practicality?

- Wolpert: Practicality is definitely an issue; pumps on the horizon are more discreet. The next generation of pumps is being miniaturized
- Nathan: Combining a separate sensor and a pump means adding another burden to patients and the undertaking is not merited with technology we have today.

Quotation that made the event

- Wolpert: "If we just withdraw into fatalistic inaction, we will never have the prospect of moving forward. That's not to deny the limitations of the current technology, but there are enough companies working at refining and improving these devices."

Ultimately, Wolpert and Nathan agreed that CGM is a fascinating technology, that technology can be disruptive, and that patients will benefit from discussion.

- **#10 AIDPIT – Igl, Austria – January 23-26, 2005**

European Association for the Study of Diabetes – Artificial Insulin Delivery and Pancreas and Islet Transplantation Study Group

AIDPIT 2005 showcased evidence of islet transplantation networks' successes, particularly in gathering enough patients for trials. The most astonishing revelation: a group in Japan had just achieved the first living related donor islet transplant, which we describe in more detail above in our notes from Geneva. Yet this news was received with some dismay by attendees, who were seriously concerned about risks to the donor of donating islet cells. Exendin-4, the analog of which is Amylin's Byetta, was shown to enhance and extend insulin independence after transplantation of a sub-optimal number of islets in a diabetic nude mouse model.

Immunosuppression in non-human primates using single or multiple doses of anti-CD154 was shown effective, especially in combination with anti-complement treatment.

Sessions on insulin use and glucose monitoring/sensing were less well attended than islet-focused sessions. Data on the use of glucose sensors in tracking otherwise undetected low blood sugars in order to modify treatment was fairly convincing. Insulin pumps are still little used in some countries like the UK, but are favored in others, such as France and the Czech Republic, where patient desire for the therapy and pregnancy are included in the indications. Inhaled insulins were compared and Mannkind's self assembling Fumaryl Technosphere insulin, which features high bioavailability and relatively quick onset of action, seemed to have great potential. The complete conference program may be accessed at

<http://www.easd.org/customfiles/easd/sg/Aidpit/FinalProgramme2005.pdf>

Top Five Sessions

- **Dr. Jean-Louis Sélam said that of the six inhaled insulins in Phase I-III trials, Mannkind's Fumaryl Technosphere product seems most promising** – but said we need four years of data to be sure. He was less enthusiastic about Pfizer's Exubera because of both the size of the delivery device (“two Coke cans!”) and the pre-determined dosage increments, which may make it difficult to fine-tune dosages.
- **Dr. A. Sharma, et al. presented an abstract on the positive effects of Exendin-4 on sub-optimal numbers of islets infused in an islet transplant**, citing significant improvement in islet function, decrease in dependence, and healthy weight gain in the short-term (<10 days) and improved early graft function and the effects continued beyond discontinuation of treatment in a 30-day study.
- **A workshop on implantable insulin pumps** offered some food for thought. Reason for using an implantable pump in type 1 diabetes: to reduce hypoglycemia. Reason to use an implantable pump in type 2 diabetes: to cope with body weight. Reason to use an implantable pump in either type 1 or type 2: quality of life. Four-hundred-fifty patients, mostly in France, Sweden and Holland, have received implantable pumps to date
 - Future priorities for implantable pump R&D
 - Insulin supply for pumps (currently only one insulin is available)
 - Reduce immunological events
 - Studies on the cost-benefit ratio
 - Extension of geographical areas of trials
 - Study of risks/benefits vs. islet transplantation
 - Need to be linked to sensors as pumps themselves don't compensate for hypo- and hyperglycemia
 - Clinics with expertise in pump use, including aseptic refills and access to surgical and radiological facilities
 - Specific funding/reimbursement for devices
 - National care centers (there are 15 centers in EVADIAC)
 - Key opinions expressed
 - On sensors – longevity needs to be improved
 - New generation of pumps need to be transplanted as an outpatient procedure and should last more than one year
 - Medtronic is working to solve the problem of aggregation and under-delivery and then will aim to expand use
 - The delay between sensor reading and insulin delivery is due to the physiological response to insulin (seven to eight mins); this is a fundamental problem. At present, “hybrid” use – manual bolusing at meals and leaving the loop closed at night – is the best option.
- **Dr. Bruno Guerci described the state of the art in glucose sensing**
 - Guerci tapped Roche's GlucOnline – presented at the EASD Symposium 2002 and the IDF in 2003 – as the most promising technology thus far.
 - (CC Note: We find his vote of confidence for GlucOnline a little surprising as we attended the IDF 2003 presentation, which was unfortunately marred by sensor drift.)
 - Guerci nominated Garg, *Diabetes Care* 2004 as the most exciting study to date.
 - Re. GlucOnline: Three-day calibration period before the sensor can be used in real time. (CC Note: This is a disadvantage in our view [What do patients want? Accurate, real-time results! When do they want them? Not in three days, ideally!])
 - A clinical trial of Medtronic's new Guardian RT Continuous Monitoring System is planned for 2005 (see Medtronic comments above)
 - Importantly, Guerci concluded that we need to learn to interpret interstitial glucose changes and connect these to clinical decision

- **Defining failure of intensified insulin therapy: algorithms to switch a patient to pump therapy and from pump therapy – Drs. Jean-Pierre Riveline & Pauline Schaepeylnck-Belicar**
 - The A1C level considered an indication for pump use in France and the Czech Republic is >8.0% despite multiple daily injections (CC Note: Compare this to 7.5% in England and 6.5% in Scotland)
 - “Unstable” diabetes, pregnancy, painful neuropathy, end-stage renal disease, insulin resistance, and quality of life are other indications for pump use
 - Reasons to discontinue insulin pump therapy
 - Patient cannot manage the pump (personally or with help from relatives or friends)
 - Ischemic retinopathy or maculopathy develops
 - Chronic skin infections
 - Non-compliance (blood glucose tests <3x per day)
 - Indications to stop pump therapy either during introductory period or annual review or when pump is due for replacement (every four years)
 - Medical reasons
 - Patient discomfort or end of a transient phase such as pregnancy
 - Ketoacidosis (incidence range of >1 to >3 in 6 months, with hospitalization)
 - Lack of A1C improvement – but this should be carefully evaluated vis-à-vis quality of life enhancement
 - Discontinuation of pump use at fourth year (replacement/upgrade time) is rare
 - **Disappointingly**, in the discussion the group agreed that doctors should pick one or two pumps for any given patient based on their assessment of the patient’s needs, not allow the patient to choose freely from all the pumps on the market (CC Note: We find this consensus disappointing – whither patient choice?)

-- by Melissa P. Ford, Jeffrey Halpern, Erin M. Kane, and Kelly L. Close

2. Conference Preview

- **Endocrine Society**, <http://www.endo-society.org>, takes place in San Diego, June 4–7. Look for lots on obesity here, including data on Amylin’s AC137 and on Sanofi-Aventis’ rimonabant.
- We’ll see you at the quilt in San Diego, where **ADA** happens June 10–14 - www.diabetes.org. It’s quite a program, as evidenced by the online search function – we are charting our agenda now!
- **AADe** meets in Washington, DC August 10–14; information is now 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, which we await with bated breath, will be up later in June on 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.diabetestechology.org) November 10–12

–by Kelly L. Close

3. More news of note ~

- **Roche Update on diagnostic business and new products** *We always write about how Roche communicates with media and analysts in more detail than any other company (by far) – this spring was no exception. Our report below stems from information we learned in mid-May during Roche’s special diagnostics update, live from Indianapolis and at Diabetes UK and AACE.*
 - **Re: FDA and approval of Bergdorf plant:** It was shared on the diagnostics call that re-inspection hasn't been done, though Roche had at that point been in intense discussions with FDA but the FDA had not committed to a date. They were to have a face-to-face meeting around the 25th of May. Heino von Prondzynski, the CEO of Roche Diagnostics division, said they have passed a very very tough internal audit and they are frustrated that they can't prove yet to FDA that they have fixed everything. They will see what date they can get. After inspection, if they pass (the assumption appeared to be that there is no question that they will pass and we would assume that it right), it will then take 6-8 weeks to garner final approval/shipping approval (we think it may not take that long but we would build in some slack). *“It’s a bureaucratic process.”* Heino noted he felt the FDA was being unfair. It was noted that the problems took 12 months to fix but that it has been a waiting game since then – they have answered a few questions, etc. It has now been exactly two years since the plant stopped shipping.
 - **Re: Overall business:** Heino made several references to the diabetes business in his diagnostics overview: 1) BGM has been weak in the US but Roche is intent on coming back with new product cycle led by Avivo. This will be launched in Germany in July and August in the US. 2) Pumps and meters will begin to speak soon. *“State of the art – combining software device that allows pumps/meters to speak – this will be in the next software generation.”* 3) Other new products will come out of the Amira acquisition, including lancing strips. Interesting – we haven’t heard about Amira in a bit. Roche appears are intent on having lancing device where no one really notices what is happening. 4) Roche will have a continuous strip by 2008/09 according to the plan. This was surprising given other comments on continuous in the session, where management stressed they do not view continuous as a threat.
 - **Re: The Roche Accu-Chek Spirit insulin pump** is waiting in the wings for its North American debut. After over two years of prohibition of speaking about insulin pumps with the US, Roche reps at the AACE appeared enthusiastic about discussing the new product, which is approved overseas.
 - Physical characteristics: about the size of a Medtronic Paradigm 712 pump; uses 1x AA battery (alkaline or rechargeable); IR port for data management; 3.15 mL user-filled cartridge; Luer lock tubing connection; 0.1 unit bolus increment; 0.1 unit basal increment; pulsatile DC motor; waterproof (IPX-8); blue backlight. Different patients want different things – we think size is a major driver of choice and Roche does not win on this front (Animas does, by a hair), but this pump is definitely an improvement over the last one and the communication options are of real interest. We understand this will be marketed in particular to a group of patients who have rejected pump therapy in the past – so not the average hyper-intensively managed patient.
 - Software: five different basal rate profiles, 24 basal rates per 24 hours; six-year lifespan from initializing the pump – then it must be returned to Roche for servicing (this was also the case with Disetronic pumps) Adjustable audio bolus increments: 0.1, 0.2, 0.5 unit.

- Interesting – the Spirit pump has three menu possibilities determined by patients or HCPs by downloading settings to the pump from a computer - this seems smart, if it is easy: 1) Standard: the things one really needs to be able to do: basals, boluses; 2) Advanced: every possible option available; 3) Custom: choose which features/options to display (using a PC to modify menu options and downloading changes to pump).
- Option of buying a two-pump set (like Disetronic did with the H-Tron pump); pricing for the two-pump set was not available at press time – we can't imagine this would be reimbursed and we always wondered about the marketing implications in sending two pumps.
- “What about smart features?” you ask. Roche has taken a different approach to offering smart features compared to the other players in the insulin pump market. Rather than incorporate carb : insulin or correction dose calculators into the pump itself, Roche has developed a software package called SmartCompass, which will allow even patients on multiple daily injections to fine-tune their flexible insulin therapy. We think that part is great – people on MDI being smarter about dosing should reduce average variability. SmartCompass will run on consumer versions of popular PDAs and smartphones. Users may appreciate the discretion of figuring a bolus while the rest of the table assumes they're composing an SMS text message. We'll have to see about the user-friendliness, which will determine a great deal in our book.
- When a patient orders a Spirit pump, he or she will be given the option to choose a blood glucose meter from Roche's range, as well as a PDA or smartphone (a smartphone would require a bit more patient investment that isn't reimbursed, but certainly the phone will have other uses). One box will arrive on the new Spirit user's doorstep, and it will contain everything needed for a pump start except for a pump-experienced healthcare provider and a supportive healthcare team.
- Concept: pump that grows with the patient's knowledge. Will be suitable for either experienced users or novices to pump therapy and will be easy for both healthcare providers and patients to understand and use.
- **Re: Blood glucose monitoring** - Roche acknowledged in its call that blood glucose market share has weakened in the US. The Advantage was launched in 1994. Since 2004, Roche has been working on successor, Accu-chek Aviva. It received 510-K approval in early May, and will launch in US in August. Throughout the remarks, there was continued reference to the winning proposition of BGM and insulin delivery - it seems that the investment hasn't stopped while Disetronic has been off the market and we'll see much more when Bergdorf is approved.
 - Roche noted (this call had lots of investors not focused on diabetes so some of it was basic) that diabetes is two different disease, type 1 and type 2. They talked about infant onset and adult onset – small point, but this terminology seemed old and reductive given the higher number of type 2 children and teens being diagnosed. Who are we to quibble, though - of course it is true that the business models that shake out from the two are very different.
 - Roche appears very focused on the insulin using consumer –type 1 and type 2 - about 15-25% are insulin using, they said – NHANES would put this higher, and we would think so too, especially with the advent of Lantus – but perhaps they were talking prandial insulin – they didn't specify but that obviously requires more testing. Those that use insulin are 29% of the patient population, they noted, but 80% of the dollar value, which is over \$2 billion of \$2.6 billion US market. That is the key driver and reason for targeting by Roche. (Sidenote: we believe the \$2.6 billion estimate is low for 2004.)

- Insulin-using patients were characterized as higher test using, a target for insulin pump business, and audience for future development (closed loop, algorithms, and “a lot of other things”) – clearly important customers.
- Knowing the consumer is very differentiating part of the blood glucose business for Roche. Clearly, consumers do influence more and more buying decisions today. It was noted that five years ago, HCPs drove over 75% of the decisions, but now consumers are driving over 40% of the decisions and this continues to increase. That appears central to their business proposition. From our perspective, we would agree about the importance of the consumer and would note that Roche is clearly investing in this, given its DTC spending, expensive (and working!) ad campaign, etc.
- Another key to the category is that there are many faces of disease. Five types of consumers with very different needs from product standpoint and HCP standpoint were discussed
 - Type 1 children
 - Type 1 teens
 - Type 2 teens (the increase in this area is due to “too much eating, tv, and gameboys”)
 - Type 1 adult
 - Type 2 adult
- It was also stated that there is more and more need for insulin pump usage – Roche will likely position pumps as very important tools once the ban increases, and the entire industry will no doubt benefit. Roche noted that people choose for a lot of reasons, but mainly pumps drive much freer lifestyle – people can eat and dose when they want to. Net net, pump therapy is a big win across the diabetes category. This is the reason that Disetronic acquisition is very strategic to them on go-forward basis, Dumoulin noted.
- One notion they kept discussing was the “circle of care” and that consumers want to be surrounded by it. The circle of care centers on collecting glucose information, analyzing information, and acting on it to drive better healthcare.
- The importance of the consumer is huge at Roche. “30% of consumers represent 80% of volume.” This group is easy to cover with mass commercial campaign. They played the commercials, which are terrific – one that features a set of twins (“True sisters from Chicago, been using products since diagnosed.”) and a new campaign featuring a mother/wife/scientist that also seems very very strong. *“I test more, I hurt less, and that’s what it is all about.”* This commercial also features language “I am a diabetic, text 6x/day,” and discusses a switch to the Accucheck Compact system.
- The diabetes portion of the diagnostics meeting closed with strategic imperatives necessary very key to regain category leadership – 1) establish renewed Accu-check portfolio (August launch of Aviva and Multiclix. New Accucheck Compact - plus monitor will have the Accucheck lancet built into monitor); 2) re-enter pump and demonstrating strategic advantage of broad portfolio (Spirit); 3) realize inherent value in customers and HCPs from implementation of circle of care. Driving better health outcomes via portfolio and COC programs is key, management stressed.

- **OmniPod Update**

- Many patients find insulin pumps a great improvement over injections, and we have a lot to look forward as pump technology continues to improve on all fronts. Insulet Corporation’s OmniPod Insulin Management System received 510(k) clearance from the FDA on January 3, 2005 and will be available by prescription in selected areas later this year.

- The OmniPod is a subcutaneous insulin delivery device that is managed with a wireless, hand-held device called a Personal Diabetes Manager (PDM), so that patients won't need to use any tubing. Insulet has also incorporated an automated insertion device, so patients won't need infusion sets or inserters.
 - In addition to adjusting insulin delivery wirelessly, the PDM will enable patients to calculate bolus dosages, monitor the operation of the OmniPod, and test their blood glucose regularly using test strips. The PDM will retain a history of all of this data, while the OmniPod gets replaced every three days.
 - You can see it on-line now at www.myomnipod.com and can check it out "in real life" at the AADE meeting later this summer, where it will be launched.
- **Medtronic** reported its fourth quarter and year end earnings in late May – below are the high points related to diabetes:
 - In prepared remarks, management alluded to a "*nice acceleration in diabetes business*" and announced the creation of a new business unit: Medtronic Obesity Solutions. It will be interesting to see where this goes. Other companies like Lilly have also been talking about new obesity businesses but it is unclear what anyone has besides Sanofi-Aventis, with its rimonabant (a.k.a. Acomplia, an endocannabinoid receptor blocker that causes weight loss) in Phase III trials (see below).
 - Diabetes growth very strong: \$178 m for the fourth fiscal quarter, up 24% year over year, reflecting Paradigm strength. Management said that an investment in training for patients and healthcare providers is yielding benefits. Goodness knows we need – badly! – better training and education. Revenues for the year were close to \$650 million.
 - Combining continuous glucose monitoring with an insulin pump has led to the Paradigm Real-time System (new name for 522/722?)
 - On the regulatory front, it sounds like Medtronic is continuing to invest in clinical trials. Early data from the European Guardcontrol trial will be released at ADA and management said the STAR-1 trial will begin soon. That will involve 140 patients; two more STAR phases will begin later this fiscal year, and will enroll 500 patients in sum. The STAR trial is another trial to further support continuous infusion of insulin (so to bolster reimbursement and coverage).
 - From Q&A, we learned that Medtronic still expects FDA approval of the Guardian RT this summer. It was submitted last August, so the question is whether or not they need a panel meeting. Even if it is based on CGMS technology, we would still assume information on how patients might use the real-time data would be desired.
 - Management refused to disclose earnings breakdowns in terms of pumps vs. disposables: "We've had growth in both." When asked if growth in the low 20s percent range is sustainable, management stated that the type 1 diabetes market for pumps is under-penetrated and this offers "significant opportunity." Yet, management admitted that "when the competition that has been outside the market comes back in, that could impact things a bit" –i.e., Roche. We believe that Roche will have excellent marketing that will help the entire industry in terms of market growth – i.e., this is not all about stealing share.
 - Although, from our perspective, the Paradigm pumps and the Spirit are not entirely comparable products, the concern makes sense, because it's one more choice for patients. Roche has always been strong in terms of managed care and it will be interesting to see watch if and how contracts change – we doubt they will change too much because patients and HCPs care about having choice on the pump front.
 - It was asked how far away the Paradigm Real-time System was from a total artificial pancreas and when Medtronic would launch a total artificial pancreas. Said Bill

Hawkins (President and Chief Operating Officer): “This is obviously a big step forward” – then Hawkins said that the near-term market opportunity is an external sensor and pump – that mimics the idea of an artificial pancreas. An implanted integrated sensor and pump are still “a ways off ...” The questioner pressed Hawkins to comment on the timeframe for the implanted “artificial pancreas,” asking, “How many years is ‘a ways off’ Two, five?” Hawkins said he would not get specific about that. We can’t personally imagine it being two or five – for us, we believe given the challenges, it’s over five for a completely implantable system that patients and healthcare providers embrace, is reimbursed, etc. For an artificial pancreas, we need an accurate, real-time, user-friendly sensor, use of a counter-regulatory hormone, working algorithms, reimbursement, etc. Art Collins (Senior Vice President and Chief Financial Officer) said they’ve looked at it and they think the largest market for an artificial pancreas is an external product, because patients are already reliant on external devices like blood glucose meters and external insulin pumps. The implantable device is still “well out” in the timeframe, apparently.

- **Sanofi-Aventis** Sanofi reported its first quarter earnings in mid-May. Although the press release had very little on the diabetes front (only a bit about Lantus success), the conference call had juicy information on rimonabant.
 - Sanofi has filed rimonabant - also known as Acomplia. Interestingly, they did not “announce” the filing; they mentioned it in response to an analyst question – very low key. They also acknowledged that they have filed for approval in Europe.
 - Earliest possible launch would be end of 2005 for rimonabant. This obviously implies some sort of fast-track action. When asked specifically about US fast track, they had no comment though they noted they have an “excellent record” with fast track.
 - They did not choose to discuss the indication(s) for which they filed Acomplia, or even with which part of the agency. They did mention that they would be positioning this as prevention for metabolic disorders.
 - They may have some sort of trademark issue with Acomplia in terms of the name. They said they would see what the FDA says. On launch details, they said they would have 500 salespeople in the US, and that this would be very complementary to other products like Lantus. Lantus is going very well, they underscored – as noted in the press release, Lantus WW sales for 1Q05 of €252 mm rose 56% from a year earlier. Q103 Lantus sales were ~\$96 mm and then \$211 mm a year later. If you use \$1.26 to the Euro, you have, call it, \$317 mm in sales for 1Q05. That is a \$1.3 bn run rate for the year, assuming it stays flat (which it won't) – but that would still be 30% up from \$1 bn in 2004. They said they expect further acceleration this year.
 - Sanofi-Aventis’ rapid acting insulin analog Apidra (glulisine) was approved last year and has only been launched in Germany – they are waiting for the pen in most geographies and this has been a real slow-down. They said the launch depends on penetration of Lantus and availability of the device – that's the real issue from what we hear from clinicians. We found it surprising that the company wouldn't have launched Apidra immediately in a vial. Apidra will compete directly with Novolog and Humalog, which had about \$2 bn in combined sales (~\$1.1 bn for Humalog, \$800 mm for Novolog) in 2004. It is said to work slightly faster and we will let you know about that when we try it! It’s been sent out already to key thought leaders – we’ll be asking and letting you know.
 - A question about the impact of Byetta on Lantus was asked. Management was complimentary of Byetta and reminded listeners that they have licensed in a product of the same class, known as AVE0010, now in Phase II trials. This was case study in how to answer a question well.

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

4. Errata and Etcetera

In our last issue of *DCU* we mentioned Frio portable cooler packs. For more information about this product, please see <http://www.coolerconcept.com> (not frio.com, as we listed).

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