DIABETES CLOSE UP

Diabetes Close Up
December 2005, No. 54
DCU on Glycemic Variability

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

From the Editor:

Excitement abounds! At year's end, it seems the focus on glycemic variability is stronger than ever. We first learned about glycemic variability from Dr. Irl Hirsch in a talk at ADA in 2003 – since then, we've learned more from Drs. Lawrence Blonde and Michael Brownlee, and we are following the area closely, as you'll see in this issue.

First, as reported widely in the news, an important piece appeared in last week's (December 23) New England Journal of Medicine *by the DCCT/EDIC study group. The article, "Intensive Diabetes Treatment and Cardiovascular Disease in Patients with Type 1 Diabetes," shows that tight glycemic control significantly reduces* macrovascular *complications based on data from EDIC, the follow-up to the landmark 1993 DCCT trial that proved that glycemic control dramatically reduced* microvascular *risk. Specifically, 11 years of follow up after the end of the DCCT (which ended early in 1993) showed that early, tight glycemic control had a major impact on macrovascular risk, lowering it by a whopping 57%. While this has long been suspected, the proof is still outstanding to see in print (especially this print), particularly as these results will be widely disseminated. At a time when the danger of cardiovascular disease in diabetes is rather suddenly – and very appropriately - receiving far more note than it did historically, this critical research again highlights the enormous long-term value of tight control. From a clinical perspective, this is undoubtedly positive – we hope that poorly-controlled patients will receive better education (following wake-up calls) in this area while the well-controlled will renew their commitment. From a commercial perspective, it's positive for literally all diabetes device and drug manufacturers (basically for* any *diabetes therapy that helps control), but for glucose monitoring manufacturers in particular since more measurement combined with instruction on what to do with the numbers is the first collective step toward better outcomes*.

A word on that. If the average *person with diabetes still only tests blood glucose, say, a little over once a day (a US centric number,*[1] *but it can't be far off globally), and the global glucose market is $6 billion, we think it would be terrific if industry could focus even more on market expansion – achieved through generating the right evidence – and less on market share, per se. We know this sounds naïve - of* course *it's a tough argument to make when every* point *of US market share is worth ~$27 million in sales, but really, it seems there should be a good opportunity to expand the market if industry did some joint marketing on the importance of testing and on what to* do *with numbers, given the new macrovascular evidence? Consider. Even if everyone with diabetes in the US just increased testing by half a strip (half a flipping strip! HALF a strip!) a day, the industry would expand by a little over a billion dollars*[2] *– let*

[1] Our math: 1) 15.8 million diagnosed patients in the US – subtract our ~15% estimate for those who do nothing to get 13.4 million; 2) multiple by 1.25x/day as our estimate on testing frequency for the other 85% (big standard deviation); 3) multiply by $0.45/strip, what we guess to be a decent estimate on average wholesale price per strip; 4) multiple by 358 days/year (assume a week off for bad behavior) to get $2.7 billion, which we believe is about the right number for US glucose monitoring industry size in 2005, about 45% the size of the global market.
[2] Our math: 13.4 million * $0.45/strip * 355 days/year *0.5 (strip) = $1.1 billion.

alone if patients agreed to test post-prandially once *a day, say, to reduce variability. But if there isn't evidence to show the dangers of variability, why would anyone try to reduce it? It is widely felt that another DCCT testing the impact of glucose variability on complications could never happen because of the cost and timing, but the costs, though hundreds of millions, would be low compared to the costs of poor clinical outcomes that could be avoid (and, as it happens, to the potential revenue for companies that sell products to improve care – which is always relevant since this is what funds more valuable R&D). Even trials testing variability using some sort of surrogate marker would be so interesting to see, given the paucity of current data. If the jury is out on the impact of glycemic instability, some evidence should be generated, no? From a patient perspective, we'd love to see more studies on variability in order to determine the clinical implications.*

Happily, considerable recent discussion has centered on the dangers and downside of glycemic variability – we'd love to see how, in the DCCT/EDIC group, the patients fared who had the same A1C but lower glycemic variability. This is impossible, however, because standard deviation of blood glucose wasn't frequently measured (once every three months, patients tested seven times a day), so the evidence is lacking. As we saw in the recent (December 19) FDA-NIH-JDRF meeting "Obstacles and Opportunities on the Road to an Artificial Pancreas: Closing the Loop" and the November Diabetes Technology and Therapeutics meetings, discussion of glycemic variability has increased significantly. In short, to us, better understanding glycemic variability is necessary to identify optimal clinical care.

As the year closes, we want to remark more broadly on the excitement in diabetes care generally. As we think about the positives, we note some fantastic new drugs were introduced in 2005 and significant progress was made on the continuous monitoring and insulin delivery fronts – so heartening! We give a mighty thank you to endocrinologists and CDEs and family and primary care doctors for continuing to try to improve care in the face of mounting challenges; also, to those making available and developing therapies and tools, thank you so much for your commitment to patients and families globally.

Our final note – we hope to continue to improve Diabetes Close Up and thank you for all your support and encouragement in 2005. Thank you in advance for filling out our reader survey, which we hope will help us move toward a better product for you in 2006. To help us, please click on http://www.surveymonkey.com/s.asp?u=348361538634

--by Kelly L. Close

In this issue:

government are working in concert to identify challenges and achieve their goals. However, we do feel that government (for now, we're going to pin next critical moves on the FDA and CMS, although we certainly recognize it's ultimately a broader team effort) just has to move on making more widely available accurate, real-time, continuous monitoring. We are hopeful that significant progress will be made in 2006. Inside, we highlight our key take-aways from the day and provide selected notes on the following:

- ***Hypoglycemia: The Barrier to Effective Insulin Therapy***
  Bill Tamborlane, M.D. (Yale University) – *Page 19*
- ***Hyperglycemia and Diabetic Complications***
  Michael Brownlee, M.D. (Albert Einstein College of Medicine) – *Page 20*
- ***What Is the Perfect Artificial Pancreas?: Nature's Specifications – Page 22***
  Richard Bergman, M.D. (Keck School of Medicine, University of Southern California)
- ***The Fast Track To Make the Artificial Pancreas a Reality for Children with T1DM***
  William Tamborlane, M.D. (Yale University) – *Page 23*

- **III. Diabetes Close Up on the Diabetes Technology and Therapeutics meeting, November 8-10, San Francisco – *page 10***
  Close Concerns attended the Diabetes Technology and Therapeutics Meeting in San Francisco November 10-12. The meeting brought together clinicians, scientists, and industry representatives interested in insulin delivery, continuous glucose sensing, and the artificial pancreas. It also offered a formal meeting space for those tackling how to set standards for continuous glucose monitors, a void that threatens to slow progress on this vital technology. We include here some of the highlights from the sessions, including our favorite, the end of meeting audience survey.

- **IV. Literature Review – New England Journal of Medicine, Intensive Diabetes Treatment and Cardiovascular Disease – *page 15*** In this review, we go through specifics of the EDIC findings, per our enthusiastic introduction.

- **V. Banting Lecture Review –** So, we know our genetic makeup has predisposed us to easy weight gain and even a biological pleasure to eating that stimulates the *same* reward centers in the brain as addiction to drugs, gambling and sex. Imagine! But now that technology and commercialism has made food so easy to obtain, adults and especially kids are gaining weight and getting diabetes a rate never seen before. So even though the environment is probably playing a huge role, understanding the genetic and molecular contributions to obesity could clearly not only help us understand why this current epidemic of diabetes is occurring, but could also perhaps lead to pharmaceutical treatments that would complement existing treatments of diet and exercise. Dr. Cullen Taniguchi gives us his observations in this inspired review of Dr. Jeffrey Flier's ADA 2005 Banting Lecture on obesity. – ***page 17***

Blogwatch - See below for blogs since our last monthly newsletter – you can see any update online at http://www.closeconcerns.com/ as well as subscribe to the blog feed.

- **December 29: Dr. David Kendall in *Diabetes Care* on the early use of TZDs**
- **December 29: DexCom in *Diabetes Care* – 10-day study shows impact of CGM**
- **December 23: JDRF names Arnold W. Donald new president and CEO**
- **December 23: *BusinessWeek* names Byetta a best product of 2005**
- **December 22: OSI pharmaceuticals grants license for DPP-IV**
- **December 22: Muraglitazar – R.I.P.?**
- **December 22: EDIC: The importance of glycemic control and macrovascular risk**
- **December 21: Amylin adds fabulous BOD member, Dr. James Gavin**
- **December 19: JDRF prompts excitement surrounding closed loop**
- **December 15: J&J buys Animas – win/win**

- **December 15: Merck – Analyst meeting diabetes and obesity details**
- **December 15: NYC to monitor patients with diabetes**
- **December 14: Arena announces positive results of Phase 2b trial for APD356**
- **December 12: Lilly and BMS – Analyst meetings diabetes and obesity details**
- **December 8: Medtronic SHAPE = Lopsided**
- **December 7: Orloff departure from FDA bodes badly for drugs at agency**
- **November 29: Dex Com Continues Momentum**
- **November 29: Consumer demand for obesity drugs real**
- **November 28: GLP-1 competition looks like it may finally emerge, in 2009**
- **November 23: Banning Surgery Below BMIs of (gasp ...) 30 in where else, England**
- **November 15: Addition of Amylin's Byetta lowers A1c in poorly-controlled TZD pts**
- **November 14: AHA Musings - Drugs and More Drugs and More on FIELD**
- **November 14: Another Complications Drug – SPP301 for Diabetic Nephropathy**
- **November 14: FIELD results negative ... no home run for Fournier**
- **November 13: FIELD trial results out tomorrow ~**
- **November 12: Novo Moves Ahead of Lilly ~ What, Six Months Only!?**
- **November 12: DT&T Day 3 - Panels, panels, panels...**
- **November 11: DT&T Days 1 and 2 ~ Continuous Update and Much More ...**
- **November 9: Sanofi 3Q05 - Mixed Quarter for Diabetes - Lantus Wins, Acomplia?**
- **November 8: Pharmacogenetics promises to predict individual drug reactions**
- **November 8: New study finds high rates of kidney disease**
- **November 8: Waist-to-Hip ratio: A new definition of obesity?**
- **November 6: CMS and Bariatric Surgery - Key Decision Coming …**
- **November 2: WSJ and Symlin - *please*!**
- **November 2: DXCM 3Q05 - Focused, calm, and fine-tuned**

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

Industry update:

1. **Merck**: Analyst meeting season is always fun for us ~ if you're only interested in diabetes goings-on, read on, we've cut through the clutter for you! Merck started off, followed by BMS and Lilly.
   - MK 431, Merck's DPP-IV, is in Phase III and has a new proposed name, Januvia. The plan is for a 2006 filing, and the company is in the midst of submitting data to ADA currently (Jan. 9 and early April are the regular and late-breaker deadlines). They ran through the efficacy results that were given at ADA, and although no new data were shown, they did show the A1C drop by A1C cohort. The A1C drop was characterized as "substantial," but on average, below 7, the drop was an anemic 0.3 (that could be rounding); from 7 to 8.5, the drop was 0.6, and over 8.5%, the drop was 1.1%.
   - In GLP-1/DPP-IV discussions, the beta cell preservation/regeneration continues to prompt significant interest. On this front, Merck showed a slide indicating restoration of pancreatic islet beta cells in mice, looking at diabetic mice, diabetic mice plus DPP-IV, and lean control mice -- showing more beta cells in DPP-IV treated mice. Of course we know the human immune system is dramatically different from the rodent one, so we'll look forward to human data …
   - As has been the case with Big Pharma the last couple of years, diabetes and obesity are now two separate areas of major focus (two of nine in this case). Merck's pipeline prioritization appears to be atherosclerosis, cardiovascular disease, diabetes and obesity. Of interest in the obesity pipeline is MK-0364, in Phase 2b. We understand that the compound is currently enrolling patients with 30-43 BMIs for a randomized, double-blind, placebo controlled two-year trial in the US and Europe. Now that's a *low* BMI floor. One red flag - similar to Sanofi's Acomplia, there is exclusion criteria for psychiatric disorders, which is pretty tough for this population since obese patients have a higher propensity for depression compared to the non-obese population and leaving out a group from trials that would likely want the drug seems problematic.
   - Merck is also working on a Januvia plus metformin drug - phase 3 started this year, and the plan is for a 2007 FDA submission. This is known as MK-431A; metformin was characterized as having a well-established tolerability (*stretch*?), efficacy, and safety profile.
   - There was absolutely no mention of Pargluva as expected, and as confirmed recently (December 22), the partnership with BMS is kaput.
2. **BMS**
   - BMS earnestly expressed its commitment to diabetes at its annual meeting, but compared to last year's, when we saw almost endless muraglitizar data, this gathering was decidedly free of diabetes data. They said nothing, literally, about Pargluva during the session except that they would decide on it *later*, which now sounds like the first half of 2006, when the company has results from ongoing trials. We know titration trials are ongoing (5 to 10 mg of Pargluva vs Actos),but we can't imagine that data will be instrumental with this decision. All ongoing trials that we're aware of are testing efficacy, not cardiovascular risk. In any event, big picture, we doubt there will be any (positive, at least) commercialization news on this drug for a long time. They probably don't know yet whether the FDA wants outcomes data; it's kind of lose-lose, really. If the FDA does want this, BMS will likely terminate. If the FDA doesn't absolutely require it, much negativity is still associated with the drug, and many others will want long-term data. Generally, we believe the safety controversy will discourage at least some physicians from trying drugs that haven't been tested in an extremely large population over a very long period of time – and by the same token, drugs with very safe profiles, like Byetta, will benefit.
   - When CEO Peter Dolan was asked directly whether BMS disputed Dr. Nissan's famed *JAMA* data (see DCU #52), he said that this same data were discussed at the panel meeting and that BMS had come to "*different conclusions*" than had Drs. Nissen and Topol. It's fascinating to watch all the parrying over the JAMA article – beyond what it said about diabetes, it focused on advisory boards at hedge funds, etc. – but from our perspective, while naturally we believe that disclosure

is crucial, the data are still the data, unsettling as they were!

- Okay, new topic, Saxagliptin: Surprisingly, almost nothing was said about this drug either. This DPP-IV is in phase 3 trials; although the company was cagey about even how many people were in the trial ("*You aren't disclosing that? ... Not at all? .... Is it 2,000 people? ... You won't say? Well, is it bigger than 1,440 people? Is it smaller than 3,800? …*") After more rounds of TQ (twenty questions), management said that two trials began in mid-2005, two more are about to begin, and two others will begin in mid-2006. Finally, when cocktails began (at 3:30!), we found a couple of members of the management team expressed a bit more excitement on this one in a restrained sort of way. Why do they like it exactly, we wondered. "*Because it appears to be a fairly well characterized molecule, the dosing looks like once-daily, the efficacy is reasonable, and the drug is well tolerated*." When pressed, actually, they seem most excited because they perceive the opportunity for this drug to replace SFUs. (Question: Will SFUs start to die a slow(er) death? We'd love to figure out to what extent they burn out the pancreas.) BMS really seems to wants to start this drug out *early* in disease progression, thus the monotherapy trials, then move it to combination; and thus they have the opportunity for a significant part of the patient lifecycle. We would guess that patients may need to move to combo therapy more quickly, because this class really only has "reasonable" at best efficacy. It's not a powerhouse, but it's decent, it's oral, they will piggyback on all the incretin education. We think *many* will want to see far more safety data (what else is being inhibited, etc.), because, as a savvy doctor always says to us flatly, "*Do you know how it works? Does anyone*?" On timing, we look for Saxagliptin Phase 2 results to be published in 2006, and some trial results to come along in 2007.
- As expected, the early stage pipeline received even less attention that the later stage pipeline. Similar to Merck, BMI identified diabetes and obesity as two major (of eight) areas of focus. In phase 1 or phase 2 are a cannabinoid antagonist (a la Acomplia), an SGLT2 lead compound, an SGLT2 inhibitor follow on, and a PPAR follow on.
- To file under can-you-believe–we-were-looking-at-something-this-small: We were curious whether Pargluva would be listed as a drug in full development. To wit. In Anthony Hooper's segment, who runs US pharma, Saxagliptin was listed under "full development" drugs, and Pargluva *wasn't*. Under Dr. Elliot Sigal's segment, both Pargluva and Saxagliptin *were* listed under full development.

3. Lilly:

- Overall, despite not a lot new to say, we thought Lilly did a good job of positioning itself as working well across a continuum - early insulin resistance, beta cell dysfunction, insulin use, complications, etc. The notable news from this meeting was that Byetta was submitted for approval in Europe. While Europe isn't exactly the best commercial environment for new drugs, we're pleased to see patients anywhere having the opportunity to use this novel new drug. Byetta has been approved in Argentina and is now eighth out of 19 diabetes products in sales. Management mentioned that patients in the Lantus trial hadn't hit a weight plateau.
- Back to Byetta: The sampling experience noted was that 70% of endos who have received Byetta have written at least one script and that half have written at least six. "*What are the other 30% doing*?" Lilly emphasized it'll continue robust sampling, and the other 30% is "*just a matter of time ... we expect to convert them*." Nice conviction! It's reasonable that the incretin pathway is not something most docs, even endos, are familiar with. Eli Lilly said the sales force *is* getting the time with docs (unusual by any standard) and that strength in script numbers by doctors often really grows after they get one patient on Byetta. The company also mentioned that patients help sell it, in waiting rooms.
- The positive Byetta -TZD study was mentioned – we'd still love to see what Byetta *plus* a TZD looks like, not just versus. In terms of expanding indications, Lilly said that a monotherapy trial was in the works, and we were reminded that it already has a monotherapy approvable letter, which is excellent. Monotherapy approval will help realize the Byetta vision as a foundational product, Lilly noted ~ DPP-IVs can't be the only drugs targeted at early use. Byetta is another

product that should be, in our view, used on the early rather than later side.

- Lilly was very positive about its insulin franchise, which was a bit surprising given the fierce competition coming with Sanofi's rapid acting analog Apidra and Novo's long acting analog Detemir. Then again, Lilly benefits just by the sheer number of people coming into the category of diagnosed PWD (patient with diabetes) and then PWDOI (on insulin). They stressed a 50/50 mix product about which we haven't heard clinical excitement. We would think detemir and Byetta would make a fantastic cocktail for those whose disease has really progressed – d is said to be weight neutral, which is very appealing.
- Regarding Arxxant, a retinopathy submission is now planned for February rather than the last quarter of 2005. They will submit with one, not two, trials, which seem to make everyone except Lilly a little nervous.
- On LAR, nothing was shared about timing for phase 3 or about clinical development pathway.
- Lilly's dual PPAR two-year studies will be done in 2006. They talked a tiny bit about a PPAR, which we understand to be an option play. Of note, Lilly has licensed a DPP-IV in phase 1 (phase 2 planned for 2007) that could have once-daily dosing.
- Regarding inhaled insulin, management said it doesn't expect a big impact in 2006, which isn't surprising. Overall, Lilly seemed a little more positive than we would have expected. A phase 3 open label study has begun in 400 non-smoking patients with type 1 diabetes – this will be 24 months with a two-month follow up period. In August, a second multi-center global trial phase 3 open-label-randomized study began, designed to evaluate safety/efficacy compare with injected insulin in 600 patients with type 1 or type 2 who also have mild-to-moderate asthma or chronic obstructive lung disease. This marks the start of a comprehensive phase 3 clinical program. The projected timeline will be given in 2006.
- On obesity, they said nearly the same thing as last year, sort of it's-a-very-important-area-etc-etc-we-have-five-wondrous-compounds-in-development...

4. **Amylin:** Amylin just announced (Dec 29) it has purchased a 150,000 square foot facility on 26 acres in central Ohio (about 45 minutes from Alkermes' Wilmington facility) to use for LAR development. Cost was $9 million, which seems like a pretty good deal – the local press said the competition had been among Kentucky, Massachusetts, California and North Carolina. Apparently the deal included over $3 million in tax credits, exemptions and grants for machinery, equipment and training – it's expected that 200 jobs will be added within five years. Amylin's clearly wasting no time, even if it hasn't officially announced that the compound will enter Phase 3 shortly. Top biotech analysts at Piper Jaffray broke this news about a week before the press release.
5. **DexCom:**
   - Flipping through (online) the January 2006 issue of *Diabetes Care* was a blast over the holidays – drinking blue bottle coffee (buy this local artisan coffee[3] for anyone who lives on caffeine - www.bluebottlecoffee.net) and looking at all the fantastic pieces. One of the most interesting was by Dr. Satish Garg, et.al., "*Improvement in Glycemic Excursions With a Transcutaneous, Real-Time Continuous Glucose Sensor.*"
   - This was the first randomized controlled trial on continuous monitoring to be published (n=91, 75 type 1 and 16 type 2, nine days), and although most of the data were presented at ADA, we hadn't seen the special breakout of glycemic data at night, where there was a 38% reduction of time below 55 mg/dL (now known to us as profound hypoglycemia), a 33% reduction of time at 55-80 mg/dL (mild to moderate hypoglycemia), a 14% increase at 81-140 (basically euglycemic), an 8% increase at 141 -240 mg/dL, and a 9% reduction at 241-400 mg/dL. Very smart to break out nighttime numbers …
   - Although this literally translates into minute differences (literally *minutes* of difference), any parent

[3] You must love this – this fledgling (if you can call anything fledgling where people are queued up 50 deep on Saturday at 8 am at San Francisco's ferry building) start-up's corporate motto is an Antoine de Saint-Exupery quote: "*In anything at all, perfection is finally attained not when there is no longer anything to add, but when there is no longer anything to take away."*

or patient can tell you that the less, the better. The 8% increase at 141-240 mg/dL was a bit unexpected, but this was only a 9-day trial. The continued hyperglycemia probably reflects "off" basal rates (or Lantus doses) – continuous would help all patients who want to improve control. The most notable line in the article was the third-to-last sentence: "*….with evidence of reduced exposure to hyperglycemia along with reduced risk of hypoglycemia, HMOs are likely to reimburse use of continuous sensors*." Check that out ~ the success of continuous monitoring certainly hinges, in our view, on reimbursement and coverage, so we're heartened by the authors' confidence (yes, seeing it in *Managed Care Weekly* might've been even more exciting, but to have the views of respected researchers is certainly encouraging). We expect approval of DexCom's STS in early- to mid-2006.

6. **Diobex**: Diobex has received word from the FDA that it has been granted fast track status on one of its two lead drug candidates, Very Low Dose Glucagon, currently in phase 2 testing. Importantly, this compound is the first drug submission ever for hypoglycemia prevention. Fast track status, of course, has no guarantees, although it does facilitate better company-agency interaction and enables companies to submit data as it becomes available, rather than in a one-time submission once all data has been generated. In turn, the FDA then can look at submissions in parts, theoretically making the entire process faster and more efficient. If anything, this news certainly suggests that that the FDA's concern over hypoglycemia continues to heighten and that the agency is searching actively for means to prevent it. In our view, only absence of hypoglycemia – and more to the point, absence of fear of hypoglycemia - will really enable tighter control across broad populations. In light of the newest EDIC data (see page 15) and FDA/NIH/JDRF conference (see below), it's become mind-numbingly clear that glycemic control must be tightened to avoid short- and long-term complications and that since it's been 13 years since DCCT (and we're worse off on the control front), the current set of tools are inadequate for success for broad patient populations. Thankfully, the urgency seems to be increasing on this front at the agency, which we hope will ultimately result in patients doing heaps better. In addition to VLDG, Diobex is also working on a compound in the newest sexy drug class, cortisol inhibitors, moving it into phase 1/2a testing.
7. **J&J/Animas:** We did a special issue on the J&J announced purchase of Animas (DCU #53) and added a few more items the day after it went out ~ the full text is now on our site.
8. **FDA**: Regarding endocrinology leadership at the FDA: It sounds like Mary Parks, who replaces Dr. Orloff in an acting capacity (she was his deputy before his departure – see our December 7 blog for more on this), has a decent chance at getting the top job there permanently. She is very highly regarded although more *other*-endo than diabetes-focused. With the incredible complexity of the disease only increasing, the FDA really also needs a diabetes person running the diabetes drugs piece, in our view, despite Dr. Parks' enormous talents. It is too much for one leader to know, no?

--by Kelly L. Close

II. DCU on "Obstacles and Opportunities on the Road to an Artificial Pancreas: Closing the Loop" This conference took place December 19 in Bethesda, MD at the NIH, which sponsored the meeting along with the FDA and the Juvenile Diabetes Research Foundation.

HIGHLIGHTS

- A number of doctors—including pediatric legend Dr. Bill Tamborlane, analytic authority Dr. William Clarke, glycemic-variability-guru-himself Dr. Irl Hirsch, complications expert Dr. Michael Brownlee and type-2-know-everything Dr. Richard Bergman—stressed that glycemic variability is an independent risk factor for complications and must be reduced. We saw from Dr. Brownlee some compelling Hirsch data showing that in the DCCT, ***of patients with the same A1C,*** those in the intensively managed group had a 2/3 risk reduction for retinopathy. This suggests something besides A1C at work – the growing consensus seems to implicate glycemic variability and the ensuing oxidative stress.

- Dr. Bergman put glycemic variability in the context of macrovascular disease and noted that although many type 1 patients today have no sign of microvascular complications, macrovascular complications are extremely common and are exacerbated by glycemic excursions. There was a focus on macrovascular complications throughout the sessions. Worryingly, Dr. Brownlee showed in non-diabetic subjects, a glucose value of 180 for only one hour led to the shut down of prostacyclin synthetase, an anti-atherosclerotic enzyme, for the next 24 hours. In a word, grim.

- The FDA received a number of questions about what it would take to get continuous glucose monitoring or an artificial pancreas approved. Three themes emerged: 1) The sponsoring company has the opportunity to define its product claim, which determines what data are necessary. 2) The FDA hopes that the science will drive the regulatory process, not the reverse. 3) The FDA is open to communication and willing to advise those working on devices early in the process. The agency noted that the device applications could (two have!) be granted an expedited review that should take between 120 and 180 days, though this depends on the quality of the application. A poor application could take as long as three years to review.

- One controversy about the closed loop is exactly what path we will take to get there: will it be incremental, or should we move directly to a fully closed loop system? We heard from advocates of both ideas, with some saying we should have a fully closed loop prototype in trials in three to four years, and others suggesting that we move first to an open loop with meal announcement (i.e., a pump where users input data about carb consumption) and proceed from there. We go for incremental, almost always, since speed is of the essence to get something out there, in our view.

- Some data on physiology in people without diabetes (called "normal individuals" <grin>) showed that physiology is actually *very* precisely controlled with almost no standard deviation. This demonstrated the magnitude and ambition of the artificial pancreas, where control is being sought in patients with diabetes who have enormous variable physiology.

- Powerhouse JDRF Scientific Program Manager Aaron Kowalski urged attendees to consider the standard of care today in thinking about the closed loop, noting that room for improvement exists across many fronts. We heard other participants echo this sentiment, cautioning once again that the perfect can be the enemy of the good.

- The technical updates on implantable sensors suggested that researchers are working on ways to create a stable internal tissue environment, avoiding the problems associated with the growth of a fibrous capsule, by promoting vascularization of the device/tissue interface.

- Dr. Bergman's presentation on the perfect artificial pancreas, focusing on "nature's specifications," raised some fascinating points about the complexity of the task. In particular, the role of free fatty acids must be considered, and a successful AP might integrate internal insulin sensors and FFA sensors. He also noted that an AP must mimic the biphasic nature of insulin release.

On our blog, we include the agenda for the meeting; continued on page 19 are our notes from presentations by Dr. Brownlee, Dr. Tamborlane and Dr. Bergman. Full meeting notes will be included in Diabetes 2006 – there is now full information on that on our website www.closeconcerns.com.

--by Katelyn L. Gamson, Erin M. Kane, and Kelly L. Close

III. DCU on Diabetes Technology and Therapeutics Meeting, November 8 – 10

Close Concerns attended the Diabetes Technology and Therapeutics Meeting in San Francisco November 10-12. Our detailed notes from the meeting that brought together more than 600 clinicians, scientists, and industry representatives are below. The meeting focused on advances in insulin delivery, continuous glucose sensing, and the artificial pancreas. We include here the program from this meeting as well as some of the highlights from the sessions and details on the survey at the close of the meeting, one of our favorite gatherings in diabetes every year.

Highlights

1. **The STANDARDS PANEL convened to get the process of standard creation rolling.** Even as the technology is evolving, the focus continues to be on FDA approval and reimbursement—what will it take to get these devices into the hands of patients? As of now, we do not have accuracy standards for continuous monitors, and many believe that a clearly defined minimum accuracy requirement for continuous glucose monitors would clarify goals for companies (especially in terms of label, which has obvious implications for commercialization) and expedite approval and reimbursement. Dr. David Klonoff, the creator of the DT&T meeting, now in its fifth year, convened a panel of thought-leaders that included clinicians and industry representatives. Overall, the industry is eager for feedback from this session, as the view has only intensified that standards are *very* much needed.

2. **Algorithms for the PSEUDO BETA CELL (excellent name, no?!) will prove challenging.** Friday afternoon's panel on the algorithm development for an artificial pancreas impressed with its complexity. The task certainly is not easy, and the next step may be what's been termed "closed loop with meal announcement," or the semi-closed loop. This is because one major obstacle is triggering insulin release in response to a rise in glucose. With current monitoring technology reading approximately between every minute and every five minutes, it would require at least ten minutes to sense a spike upwards, and the slowness of subcutaneous insulin would amplify this lag. Studies blocking first-phase insulin release have shown that this delay wreaks havoc with post-prandial glucose control, and we know that timely insulin release is a key to glucose control, so a closed loop system will need to solve this problem. One intriguing finding from this meeting was that Mannkind's Technosphere, which appears to work more quickly than any of the rapid-acting insulin analogs, is soluble at a pH of 7, which may mean that it could be taken subcutaneously. Although there is some obvious irony if this insulin is, in fact, as fast as it appears, subcutaneous use may be welcome indeed.

3. **Early DIAGNOSIS may soon be easier.** We were intrigued by newly funded VeraLight's presentation. Its non-invasive system measures advanced glycation endproducts (AGEs) and could be used to diagnose type 2 patients. The two methods currently used are oral glucose tolerance tests, which are inconvenient, requiring fasting, etc., and fasting plasma glucose, which has a sensitivity of only 50%. The first method can be difficult for patients and providers (time consuming for both, not always reimbursed, etc.) VeraLight's product, known as Scout, uses "noninvasive skin fluorescence spectroscopy"; it is enrolling a 700-person trial now. With an estimated 6.2 million people currently undiagnosed in the US alone, we envision this non-invasive device next to the blood pressure machine in the drugstore…and actually, beyond that, we are intrigued by its potential use in diagnosing complications, which was raised by Dr. Bruce Buckingham. We wonder if in time use of the test could actually help prevent complications.

4. **The ARTIFICIAL PANCREAS session brought new data on continuous monitoring**. This session began with a presentation by **Dr. Martin Ellmerer** of the **Medical University of Graz, Austria,** on in-hospital closed loop systems, and **Dr. Moshe Philip** presented **Medtronic**'s GuardControl results that we reported on from EASD, highlighting the 1.1% drop in A1C seen after

90 days of wearing the continuous monitor, from a baseline of 9.6%. Although that baseline is high, the results undoubtedly could be much better once patients and providers learn more about the system, get more used to it, and determine how to use the data optimally. The main *new* data on continuous monitoring was on the Navigator. **Dr. Tim Goodnow** of Abbott Diabetes Care highlighted the progress of the past year. We were impressed by the improved accuracy (mean absolute relative differences now around 11-13%) and longer 5-day wear period (said to be a result not of a change in sensor chemistry but rather of improved adhesive). He also discussed briefly the 10-hour lead in required before real-time readings. The Navigator, of course, is at the FDA now, along with DexCom's STS. The Guardian RT was approved in late July. We can't wait until we can have our very own real-time sensors – the reimbursement will likely be the toughest part and on that front, we're glad to see all companies moving forward with trials. Dr. Buckingham said it all in his open statement to the FDA and payors, when he emphasized that the technology was usable, understandable, and will dramatically improved lives, due to substantially fewer hypos. "*Approve and reimburse*" seemed the unspoken imperative.

5. **The open session on STANDARDS combined very useful academic and industry perspectives.** The 10-minute length of these presentations was frustratingly brief but allowed for a long list of knowledgeable speakers. Carol Herman of the FDA moderated the academic section. **Dr. Steven Gutman** first presented "FDA and the Regulations of the New Generation of Glucose Measurement Devices." He presented some of the challenges to FDA regulation of continuous glucose questions. In a list of unanswered questions, he included 1) what is acceptable performance?; 2) how do you measure trade off between increased data and difference in data?; 3) what do the differences between different types of fluids mean?; and 4) how do you measure and compare changes in signal? The industry perspectives section began with **Geoff McGarraugh** of **Abbott Diabetes Care** on "Determining the Accuracy of Insulin Adjustments Using Continuous Glucose Monitoring." McGarraugh evaluated the clinical accuracy of the continuous sensor by examining differences in insulin dosing decisions. **Dr. Donald Parker** of **Bayer's** "A Stake in the Ground for Clinical Efficacy" emphasized the importance of accuracy, expressing concern that discussions are focusing too exclusively on clinical practice guidelines. **Dr. Barry Ginsberg** of **Becton Dickinson** presented "Measuring Accuracy in Continuous Glucose Sensing," proposing a Bayesian statistical approach to assess accuracy that would reflect biological constraints – i.e., physiology - of the system. In a presentation titled "A Continuous, Noninvasive Glucose Monitor," **Dr. Benny Pesach** of **Glucon** gave results from accuracy studies of a non-invasive device based on photo-acoustic technology. **Dr. David Horwitz** of **LifeScan** spoke to "Consideration for Standards in Continuous Glucose Monitoring," looking conceptually at how a standard could be established. **Dr. John Mastrototaro** of **Medtronic**'s "Performance Standards for Continuous Glucose Monitoring" asserted the need for multiple metrics of measurement and stratification by glucose range within these metrics. **Ms. Luann Ochs** of **Roche** presented on "Successful Standards Development—How to Avoid Obstacles and Setbacks."

6. **INPATIENT glycemic control can lead to dramatically improved outcomes.** As we always do,[4] we looked on in awe as **Dr. Anthony Furnary** of the Starr-Wood Cardiac group in Portland presented his hospital's stunningly low mortality rates for cardiac procedures in patients with diabetes. Diabetes patients usually have what Dr. Furnary termed the "diabetic disadvantage"— this results in two times higher in-hospital post-operative mortality, four times higher infection rates, and longer lengths of stay, and considerably higher costs. The program at his hospital, however, known as the Portland Protocol—a program to tighten glycemic control in the hospital—has brought mortality in diabetes patients down to 0.9%, compared with the national average of 3.9% for diabetics. Dr.

[4] We've seen Dr. Furnary present on Portland data multiple times, though as the data is always updated, the awe continues as his perspective on the importance of control is reinforced again and again.

Furnary stressed that the most important predictor they found in the Portland diabetic project was "3BG" or the average 3-day post-operative blood glucose. To achieve those rates, they used a continuous intravenous insulin protocol and measured glucose very frequently, ranging from every 30 minutes to every two hours (either by arterial line drop, venous line drop, or fingerstick), depending on glucose level and rate of change. This problem - bad glucose control in the hospital - is mighty, and we believe Portland is the model for approaching care aggressively and lowering costs exponentially. How excellent is it that patients with diabetes actually did *better*, not worse, that non-diabetics, in this hospital! Stay tuned for publication of the Portland data. We believe that thought leaders across the country recognize Portland's progress, but given how fragmented the hospital system is, it will take a great deal even to get such standards recognized in the ICU alone – much less the rest of the hospital (critical care, labor, etc.). Still, the momentum is going full steam ahead on this front, and a meeting on implementation sponsored by AACE in January should be helpful – and we think the real changes will take place once JHACO creates its own standards, which we look for in the coming few years.

7. **NONINVASIVE monitoring made its presence known.** The large presence of non-invasive monitoring at this meeting was surprising – interest has definitely reemerged. We heard from **Dr. Wayne March** (State University of New York Downstate) on "A Noninvasive Contact Lens Glucose Sensor: An Application of Ocular Spectroscopy," **Glucon**'s **Dr. Benny Pesach** on "A Continuous, Noninvasive Blood Glucose Sensor," and **Dr. Orna Amir** on **OrSense**'s progress. **Dr. Mihailo Rebec** of **Bayer** presented a talk titled "Characterizing the Time Lag Contributions to Transdermal Continuous Glucose Monitoring." Bayer licensed a technology from **Sontra Medical** some time back, and Dr. Rebec differentiated transdermal monitoring from continuous, noting both advantages and disadvantages. Noninvasive has historically faced significant challenges in isolating the glucose molecule in detection and filtering out noise. Glucon and OrSense also both offered new data at this meeting.

8. **The session on HYPOGLYCEMIA was one of the strongest. Col. Karl Friedl** moderated the segment on hypoglycemia, which featured some top researchers, beginning with **Dr. Robert Sherwin** of Yale on "Brain Interstitial Fluid Glucose: Effect of Hypoglycemia." These surprising data showed that, in rats with recurrent hypoglycemia, there is an enhancement of glucose across the blood-brain barrier during tasks, an adaptation that is not seen in rats that have not been exposed to hypoglycemia. **Dr. Brian Frier** of Edinburgh presented on the "Consequences of Recurrent Exposure to Hypoglycemia in Type I Diabetes," looking at how levels of glycemic control and exposure to hypoglycemia and hyperglycemia change the level at which counterregulatory hormones are released. **Dr. Anthony McCall** of UVA addressed "Hypoglycemia Unawareness and Hypoglycemia Risk Prediction," focusing on how one might predict and detect hypoglycemia. An index called the "low blood glucose index" has been found to be a strong predictor of hypoglycemia. Dr. McCall stressed, "Current estimation, on some level, is a trivial issue" and noted the need for prospective data and predictions that could be provided with continuous monitoring. **Dr. Nejhdeh Ghevondian** concluded with "A Novel Noninvasive Methodology for the Detection of Hypoglycemia," a discussion of the 'HypoMon' product that measures heart rate, QT-interval and skin impedance as indicators of hypoglycemia.

9. **The U.S. Army's Technologies for Metabolic Monitoring program is working toward continuous monitoring as well.** The "Technologies for Metabolic Monitoring" session was moderated by **Lt. Col. Carl Hover**, and **Dr. Jeffrey Sutton** of the National Space Biomedical Research (NSBRI) delivered the keynote address, "Medical Technologies for Space Exploration and Diabetes Management." The address defined the points of the NSBRI's agenda and the goals common to the diabetes field and the NSBRI. Also in this session, **Mr. Philip Stout** of **LifeScan** delivered "Reproducibility of Interstitial Fluid Glucose Lag and the Relationship Among Lag, Lag

Mitigation and Peripheral Blood Perfusion." **Dr. Volker Lodwig** of Sweden concluded with the results from the ROSSO study in "Self-Monitoring of Blood Glucose in Type 2 Diabetes is Associated with Improved Long-Term Outcomes: The ROSSO Study." The retrospective study analyzed 3,268 patients over a period of 6.5 years. The study found that type 2 patients using SMBG had a 32% reduction in non-fatal endpoints and a 52% reduction in fatal endpoints.

10. The insulin delivery session was extremely interesting; **Dr. Matt Riddle** suggested how valuable continuous monitoring would be and also the *combination* use of GLP-1 and insulin – quite intriguing! The presentation on Technosphere by Dr. Leone-Bay that followed was also interesting given control post-lunch for type 2 patients – perhaps dosing won't be necessary, which would be at least a minor breakthrough.

Finally, the annual Diabetes Technology survey has been a highlight of this meeting every year, and this year was no exception. Dr. John Pickup moderated the survey and those discussing it included Dr. Dorian Liepmann (UC Berkeley), Dr. Bruce Buckingham (Stanford), Dr. Aaron Vinik (E Virginia Medical School, Norfolk, VA), and Dr. Jan Wojcicki (Institute of Biocybernetics, Warsaw, Poland). Although putting this at the end of the conference always means that a number of clinicians have left (and there's the problem of industry votes that don't reflect true physician beliefs), it is fascinating to hear from the experts. This year, the following questions were asked, with the percent answer following each choice, and comments from panelists (and CC) following. Between 100 and 130 votes were received for each answer. Some of our favorite questions:

- **Which of these technologies under development is most needed?**
  - Noninvasive monitoring: 22%
  - Real time CGMS: 33%
  - Artificial pancreas (that requires patient determination of bolus at mealtimes): 11%
  - Inhaled insulin: 3%
  - Computerized and individualized case management software: 8%
  - Higher accurate hypoglycemia detection device: 23%
  - Interestingly, 56% of respondents said real-time continuous or a hypoglycemia detection device, which reflects the desire to reduce further glycemic variability. Dr. Pickup voiced surprise at not receiving more votes for the artificial pancreas – the pseudo beta cell, as it were – and Dr. Buckingham said he prefers the artificial pancreas. We suspect if it came right down to it, *many* would prefer it (perhaps the entire audience?), but the votes for other technologies (such as real time CGMS, which is basically a part of the AP) indicated a desire to have those first, and probably some doubt when the AP will actually emerge.
  - It was asked that someone (of the 3%) who voted for inhaled insulin come forward and discuss the choice, but none did. Dr. Barry Ginsberg (Becton Dickinson) noted persuasively that the vast majority of type 2 patients are on oral agents and two thirds are not at A1C goal. He argued that more need to go on insulin, given that the average delay is four years (four years!) from the time they are first told to go on insulin and when they do.
  - The significant percentage – 22% - of those that voted for noninvasive was notable and certainly indicates, still, a desire for each glucose monitoring.
  - From the audience, Dr. Grodsky noted his major takeaway from the meeting was how far the continuous glucose monitor has come! Another audience member remarked that he could do almost as well with the software, and it is much cheaper than the other choices – the audience remained unconvinced.
  - Dr. Vinik made his case for why the real-time continuous was needed. He mentioned that for type 1 patients, while A1Cs had improved from a mean of 9.2 to 7.5, that better post-prandial glucose scores were the barrier to get to 6 or 6.5%. He wants something to measure easily and make adjustments, so he voted for continuous. *CC comment: for the right patients, Symlin*

really works on post-prandial values like nothing we've ever seen – while continuous can alert one to a situation one must correct – and we're dying to have this capability! Symlin is fantastic because it actually helps avoid the situation (high post-prandials) in the first place. We note that it has to be carefully used, and we suspect that many more people might use Symlin once real-time easy reimbursed continuous is available and titration becomes easier to manage.

- Dr. Vinik made a very important point about the fear of insulin, namely that this fear is associated with two factors – fear of insulin itself and fear of injections. He mentioned that on average, there is a 23 to 25-month wait in moving from metformin to insulin and 35 to 36 months in moving from a sulfonylurea (SFU) to insulin. He estimated each factor as contributing to about half the delay.

- **What is the main barrier to widespread adoption of tight glycemic control in hospitals?**
  - Lack of accurate continuous sensors: 25%
  - Lack of effective algorithms of software to control insulin therapy: 12%
  - Risk of a sharp increase in incidence of inpatient hypoglycemia; lack of money for more nurses or more inpatient programs: 15%
  - Lack of money for nurses: 25%
  - Inadequate evidence to warrant a big increase in hospital resources: 7%
  - Lack of a commitment to initiative by doctors: 16%
  - *CC comment: This was an interesting one. We think the main barrier to widespread adoption of tight glycemic control in the hospitals is the same reason for the main barrier of tight glycemic control in outpatients – absence of the best tools, and related education and reimbursement matters. Now in the hospital this is more complex due to staffing, of course …*
  - Dr. Buckingham pointed out that the evidence certainly exists to show that outcomes with optimal glycemic control are certainly far better.
  - Dr. Jeff Joseph said that #1 is "*by far the answer*" because there is overwhelming evidence that tight glucose control around stressful events leads to improved outcomes. In the hospitals, that therapy is limited to a select few people, depending on staffing. He explained a bit the intensity of the environment and voiced his option that implementing tight control without causing hypoglcyemia was very difficult currently and that a tool that automates monitoring with alarms would be a major benefit. "*This is going to happen sooner than you think...*" he concluded.
  - We also wonder about reimbursement; it sounds like this will be kick-started if/when JCAHO, which is the Joint Commission on Accreditation of Healthcare Organizations (www.jcaho.org), makes glucose-value documentation a criterion.
- **How many years until an artificial pancreas emerges?**
  - Five years: 12%
  - Ten years: 65%
  - 25 years: 20%
  - 50 years: 1%
  - 100 years: 1%
  - Over 100 years: 1%
  - In discussing barriers, Dr. Vinik said he believed most people think the absence of good algorithms/system is the problem.
  - Dr. Pickup said that he was in the 25-year camp: "*This is fantastically difficult problem given we don't have sensor with any degree of accuracy and/or that is suitable to use for home use. To say nothing on algorithms …*"
  - Said another participant: "*People have been struggling to get a sensor to work for last 25 years – that is, getting it to work in safe manner in routine use – that's a tall order. So I'm surprised to see nearly 80% of us expect to see this in ten years or less!"*

- Dr. Barry Ginsberg pointed out that NEHI did an elaborate six-month survey on this question and found that most experts looked for an artificial pancreas between 2014 – 2018.

- **What is main barrier to development and adoption of an artificial pancreas?**
  - Lack of sufficient sensor accuracy: 68%
  - Algorithms do not simulate normal physiology sufficiently: 12%
  - Insulin delivery is not physiologic into skin and delivery technology is too risky for delivery: 7%
  - One-way control leads to hypoglycemia: 6%
  - Too much hardware for patients to agree to use: 0%
  - Cost will be prohibitive for most interested patients: 7%
  - Dr. Buckingham pointed out that even if the sensor isn't that accurate, patients could figure some version of useful control - at least, better than we have today!
  - Dr. Grodsky says figuring out the sites and cleaning up the algorithms are the major practical problems.
  - Dr. Roman said that sensor accuracy was not as big a problem as sensor reliability.
  - Dr. Joseph said that if we could get to a sensor in real time, then we would have an AP in a short period of time. "*If they can land a man on moon and 747s can be landed automatically – they can do a sensor. New insulins will have rapid on/rapid off kinetics. We'll have insulin delivery catheters that are implanted permanently – we're moving to address absorption issues. What is missing is the sensor*."
  - Dr. Ginsberg expressed some doubt: "*Skills can replace a body part …when you look physiologically where you have an instantaneous sensor and instantaneous absorption – you still need to address eating. Even with rapid insulin and rapid sensor, it will be hard to get tight control*."
  - Dr. Bruce Buckingham addressed an important question: "*How do we define what we want the artificial pancreas to do? Prevent long-term complications? Prevent hypoglycemia? We're close! Let's look at improving life, not absolutely mimicking the beta cell. No one here is as smart as a beta cell …*"
  - We weren't even sure of the definitions….
- **Do you see a need for a small patch-type insulin pump that can pump one infusion rate only?**
  - Yes: 18%
  - Yes, but only if cheap and easy to use: 27%
  - No, because bolus infusion capability is a must: 15%
  - No, because basal must be adjustable to be useful: 24%
  - No, because market for pump that has fewer features than current will be too small: 6%
  - No because time release insulins have rendered pump therapy too small: 9%
  - Dr. Pickup said that in principal, one rate would be suitable for type 2s and many type 1s and argued for #2 as the right answer.

--by Erin M. Kane and Kelly L. Close

IV. Literature Review – *New England Journal of Medicine* on EDIC Results

DCCT/EDIC Study Research Group. "Intensive Diabetes Treatment and Cardiovascular Disease in Patients with Type 1 Diabetes." NEJM. 22 Dec 2005. 353(25): 2643-2653.

This issue of the *New England Journal of Medicine* highlights what we believe represents the most important research findings of the year in diabetes – the recognition of how tight glycemic control affects macrovascular risk.

These data are striking because they indicate that **intensive treatment – reducing A1C levels by 1% -- lowered the risk of any CVD event significantly – up to 57%.** As you may recall from the DCCT, a 1% drop had reduced microvascular risk by ~ 25%. Thus, these EDIC results not only reinforce the importance of tight glycemic control but also confirm the imperative of getting patients under control *early*. Over the years, the two groups from the original DCCT study have converged in their control – both now have A1Cs around 8. Those who were initially *intensively* treated had far less cardiovascular disease than those in the control group. We find this concept of "metabolic memory" very intriguing – the body, for whatever reason, "remembers" blood sugar levels for many years so that high glucose levels today can increase the risk for complications far down the road. Certainly, this would argue for heightened efforts to achieve tight control.

As the EDIC results have reconfirmed the importance of lowering A1Cs, some question whether we should lower our targets. As Dr. Nathan said in a recent note: "*Patients and health care professionals should remember that the intensive therapy goals in the DCCT were normal blood sugar and HbA1c, less than or equal to 6.1%. We pursued this goal and achieved a mean HbA1c of about 7%. Therefore, a goal of 7% that has currently been set is likely to result in HbA1c levels higher than were achieved in the DCCT. Patients and their health care providers should aim for the lowest HbA1c level that can be safely maintained. Factors such as relatively short life expectancy, hypoglycemic unawareness and repeated episodes of severe hypoglycemia, and occupations that might make any hypoglycemia more hazardous, will temper the HbA1c goal, which needs to be individualized for all patients*."

However, Dr. William Cefalu, who wrote an editorial accompanying the paper, says in a piece reported in the *New York Times* that it is difficult to convince people to adhere to intensive therapy, defined as four shots a day. That is an interesting perspective, since it comes at a time when real-time accurate continuous monitoring is all the rage. Will control improve when patients are actually aware of – and regularly reminded of – the implications of poor control? We think seeing the numbers will make a difference – if continuous fulfills its promise, patients will have a valuable tool that will make it easier and faster to correct hyperglycemia and hypoglycemia, or even avoid it in the first place. Too, Symlin will help facilitate reaching glycemic targets in the future, as the drug helps curb the post-prandial highs that many patients find so troubling to correct (and just troubling, period).

Interestingly, Dr. Cefalu questions whether current glycemic targets are too high and essentially arrives at an impasse, noting that most patients have not met those targets. He questions what lowering the goals further would do. We would think that A1C targets should be lowered if evidence shows the lower the better – which it does – but we don't think targets should be lowered until they can be reached *safely*, i.e., until hypoglycemia isn't an immediate danger. Hypoglcyemia is clearly the largest barrier to tight control; as such, we believe more focus and funding should be put on reducing the glycemic variability. Noted Dr. Bernard Zinman, member of the DCCT/EDIC study research group, in a recent chat, to cap it off: "*The DCCT/EDIC results clearly demonstrate that the initiation of intensive diabetes management early in the natural history of type 1 diabetes will have a prolonged and sustained effect not only on the microvascular complication but also the devastating macrovascular consequences of diabetes. Intensive therapy is now the standard of care for patients with type 1 diabetes. Based on the magnitude of the beneficial effects of intensive therapy the health and economic impact will be enormous.*"

The question of whether the EDIC analysis could be extended to type 2 patients arose immediately when Dr. Nathan delivered these stunning results last June. Although there isn't evidence yet, we believe that trials coming in the next few years, specifically ACCORD and BARI-2, will show that the results can be extended to this larger group of patients, the type 2s. And on to our review!

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--by Katelyn L. Gamson and Kelly L. Close

V. Dr. Cullen Taniguchi on the 2005 Banting Lecture

Ed. note: The following article examines Dr. Jeffrey Flier's Banting Lecture at the American Diabetes Association meeting in San Diego earlier this year. We found this piece particularly interesting as so much is written on environmental factors related to obesity but far less on biological effects. Kudos to ADA for making it possible to listen to the actual lecture itself – webcast! – on the organization's website www.diabetes.org. We encourage you to do so ~ in tandem with reading Dr. Taniguchi's take, we think there's significant learning potential here even for those currently immersed in the field.

No risk factor is more important to the development of type 2 diabetes than obesity. The numbers are scary. For instance, a person with a body-mass index (BMI) of 35 (moderate-to severely overweight) has a 100 times greater risk of developing diabetes than a person who is not overweight. And it's not just diabetes. Obesity leads to many medical conditions, including cardiovascular disease and cancer.

Not surprisingly, a tremendous amount of research has been initiated over the years to try to understand the causes of obesity. It might *seem* a simple problem of eating too much, or a lack of will power, but of course we know the issue is far more complex. Weight management is perhaps the most obvious battle of nature versus nurture; that is, the two most important factors that influence obesity are your genes and your environment. The environmental causes are well known: cheap and easy access to food, the quality (or lack thereof) of food eaten, and sedentary lifestyles. The biological mechanisms that underlie the drive to eat, as well as to overeat, are not as clear, however. In what was one of the most interesting and complex talks of this year's ADA, this question was investigated by Dr. Jeffrey Flier, who was awarded the 2005 Banting Medal for his work on understanding the molecular and genetic basis of obesity.

The Powerful Hypothalamus

Dr. Flier is most interested in the biological signals that regulate our eating patterns. For over 70 years, it has been known that the regulation of appetite and satiety is controlled principally by a region of the brain called the hypothalamus, which integrates many hormonal cues (whether you have just eaten, expansion of the stomach) to determine whether we reach for an extra holiday treat. In addition, the hypothalamus responds to the pleasure of eating. The sensation evoked by eating can tap into the same pleasure centers of the brain that give the sensations of happiness while, unfortunately, also mediating addiction. These "hedonic signals" are as powerful as any physiologic mechanism of appetite and satiety, and contribute significantly to eating patterns. Over many decades, neuroscientists, physiologists and endocrinologists have all indicated that the brain plays a critical role in regulating obesity. Dr. Flier's research has concentrated on whether the brain is autonomous in controlling appetite or if it works in conjunction with other tissues in the body. The discovery of the fat hormone leptin shed light on this fascinating biological question. Fat cells, or adipocytes, are those much-maligned cells that store depots of excess energy. Until a few years ago, adipocytes were just thought to be the body's Tupperware—storing extra nutrients until we needed them. However, it is now known that fat cells secrete hormones that inform other tissues about the nutrient status of the body. In times of nutrient excess, the hormone leptin is secreted by adipocytes to signal to the brain to curb appetite. Leptin also enhances the burning of fat molecules in other tissues, most notably in the liver. Because of these very powerful effects on metabolism, leptin has been recognized as an important regulator of body weight, since it controls both the intake of food and the use of food already stored as fat.

Although the biology has been thoroughly studied in mice and other animals, the role of leptin in human obesity and diabetes is still not clear. There are rare human syndromes in which patients do not secrete leptin due to a failure to develop adipocytes (lipodystrophy) or a general lack of leptin. These patients become massively obese, which can be reversed completely with recombinant leptin treatment. These

successes made the promise of leptin therapy for diabetes seem plausible, but much to chagrin of scientists, most obese humans were found to already have high circulating levels of leptin. Although one would expect that these elevated leptin levels in the blood would curb appetite and increase fat oxidation in the liver, this is often not the case. Dr. Flier and many other scientists hypothesized that some mechanism must exist by which leptin is not working properly.

This phenomenon, called "leptin resistance," is now known to be common in obesity and is being better understood at the molecular level. Although several mechanisms could be implicated in leptin resistance, Dr. Flier has focused on the cellular signaling pathways that occur after leptin binds to its receptor in the hypothalamus. Leptin is known to bind to specific neurons in a region of the hypothalamus called the arcuate nucleus. Since leptin is a catabolic hormone (it suppresses appetite and promotes the breakdown of fat), it activates the pro-catabolic neurons of the arcuate nucleus (POMC and CART) and inhibits the pro-anabolic neurons (AgRP and NPY neurons) in the same region.

To understand how cellular function is altered by signals mediated by the leptin receptor, Dr. Flier studied several aspects of the leptin receptor, which is in the same family of receptors used by cytokines, which are hormones of the immune system. Not surprisingly, the leptin and cytokine receptors use similar cellular pathways to transmit its signal. For instance, the molecule STAT3 (Signal Transducer and Activator Transcription) is phosphorylated by a component of the activated leptin receptor known as JAK2. STAT3 then is then shuttled to nucleus of the cell where it binds to DNA to activate the transcription of many genes necessary for the leptin response (as its name implies). One of these genes induced by STAT3 is called the SOCS3 (Suppressor Of Cytokine Signaling), which powerfully inhibits the functions of STAT3, and therefore leptin. Although at first it might not make sense for leptin to upregulate an inhibitor of its own signal, the SOCS proteins serve an important function to turn off the leptin signal at the appropriate time (otherwise you'd never eat). Unfortunately, in states of obesity and diabetes, the SOCS proteins are expressed at higher levels than normal, and therefore leptin becomes less efficient in activating its normal cellular pathways.

Dr. Flier's lab used gene knockout techniques to eliminate the SOCS3 gene in mice and found in all instances that leptin's actions were enhanced; mice with less SOCS3 ate less than mice with normal SOCS3 expression. Further experiments using SOCS3 knockouts that were limited to the brain also showed enhanced sensitivity to leptin. That is, mice that lacked SOCS3 only in the brain lost significantly more weight when they were injected with leptin than control mice that had normal SOCS3 expression. These experiments demonstrated that leptin action on the brain is critical to regulating appetite and body weight.

The next logical question is why SOCS3 levels are higher in diabetes. One physiologic substance known to induce the expression of SOCS3 is free fatty acid, levels of which are often elevated in obesity. Dr. Flier's group and others cleverly noticed that free fatty acids resemble the molecular structure of lipids on the outside of bacteria that cause an immune reaction (lipopolysaccharides). When these bacterial lipids bind to special receptors in the immune system known as toll-like receptors (TLR4), they activate a signaling cascade that increases the expression of several genes, including SOCS3! This led Dr. Flier to hypothesize that toll-like receptors might be present on non-immune cells, and that increased free fatty acids in the blood from obesity might be inadvertently activating the immune pathway and inhibiting leptin's functions. Indeed, Dr. Flier showed data that TLR4 knockout mice showed a decreased immunological response to bacterial lipids and a decreased metabolic response to dietary lipids.

Dr. Flier finished his lecture by touching on some other areas of important research. The first was the discovery of melanin concentrating hormone (MCH), which causes mice to eat insatiably. Knockout mice lacking MCH ate much less food and lost significant amounts of weight. The loss of MCH expression could also reduce weight in several severe forms of rodent obesity. Thus, MCH antagonists

have been developed, and they appear to substantially lower weight in obese mice. No data regarding human trials were mentioned.

Finally, Dr. Flier posited that certain hormones in the body might work by altering the physical connectivity of neural networks. The hormone ciliary neurotrophic factor (CNTF) is a known trophic factor for motor neurons and was thus a promising therapy for amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease). Although the clinical trials of CNTF did not succeed in treating ALS, researchers noted that patients treated with CTNF developed anorexia and weight loss. The most interesting aspect of the CNTF treatment was not that the subjects lost weight, but that they kept losing weight even after the treatment had ended. This led Dr. Flier's lab to investigate whether CNTF could alter the way the neurons were hard-wired to each other. Many years of research led to the discovery that CNTF not only activated the neurons that suppressed appetite but also stimulated the growth of new neurons from stem cell progenitor cells. These new cells became wired into the existing networks that regulated appetite, leading to the continued enhancement of the anorexic signals well after the CNTF treatment ended.

Dr. Flier's work is significant not only for its impact on the biology of appetite and obesity, but also for changing the perception of obesity as a medical disorder. Although availability of unhealthy fast food or the emotional satisfaction of eating contributes to obesity, the research from the Flier lab has shown that human biology also plays an important role in regulating body weight. While their work may lead to new treatments for obesity, it will hopefully also contribute to a better understanding by the public that obesity not simply an issue of will power. It also reflects complex biological systems hard-wired into our brain through millions of years of evolution.

--by Cullen Taniguchi

"OBSTACLES AND OPPORTUNTIES ON THE ROAD TO AN ARTIFICIAL PANCREAS: CLOSING THE LOOP" - *continued from page 9*

Hypoglycemia: The Barrier to Effective Insulin Therapy
Bill Tamborlane, M.D. (Yale University)

Dr. Tamborlane began by reminding us of the trade-off between glycemic control and hypoglycemia: aggressive therapy reduces the risk of micro- and macrovascular complications at the cost of an increase in the risk of hypoglycemia. **More than half of hypoglycemic episodes occur during sleep, and continuous glucose monitoring data show that *asymptomatic* hypoglycemia is surprisingly common during sleep, especially during intensive insulin treatment.** Among patients with type 1 diabetes, the fear of hypoglycemia is sometimes even greater than the fear of complications, and according to Tamborlane, what patients and their families do not know is that the hypoglycemia they see is probably "just the tip of the iceberg." Insulin pumps and insulin analogs may reduce hypoglycemia, but they do not prevent it.

Non-diabetic individuals have a multi-tiered defense system against hypoglycemia that includes: 1) suppression of endogenous insulin secretion, 2) secretion of counterregulatory hormones such as glucagon and epinephrine, and 3) subjective awareness of hypoglycemia. Non-diabetic individuals are exquisitely sensitive to small reductions in glucose. However, type 1 patients have no way to suppress the effects of insulin once it is injected, due to the loss of endogenous insulin, the loss of glucagon response to hypoglycemia, and the impaired epinephrine response associated with intensive therapy. Paradoxically, the introduction of CSII in 1979 led to the appearance of hypoglycemia unawareness. This problem was recognized in the first patients to receive outpatient insulin pump treatment: pre-pump hypoglycemic symptoms occurred at a maximum blood glucose level of 65 mg/dl, while post-pump hypoglycemic symptoms only appeared at a blood glucose level of 50 mg/dl.

As early as 1925, Dr. Banting noted in his Nobel Laureate lecture: "As a patient becomes accustomed to a normal blood sugar the threshold of these [hypoglycemic] reactions becomes lower." Nearly two decades ago, Amiel, et al. (NEJM 316: 1376, 1987) demonstrated that intensive diabetes treatment induces the loss of the body's natural defense mechanisms against hypoglycemia. In their study, the blood glucose level of eight non-diabetic patients and 10 poorly controlled patients undergoing low-dose insulin infusion stabilized around 60-70 mg/dl due to an increase in glucose production by the liver. However, among the 11 patients with well-controlled diabetes on pump therapy, hypoglycemia developed during insulin infusion, and the blood glucose level did not stabilize until ~40 mg/dl. In these 11 patients with well-controlled diabetes, there was a much lower threshold of glucose that triggered release of epinephrine (<45 mg/dl vs. >55 mg/dl in the non-diabetic and poorly controlled diabetic groups). Moreover, in four of the poorly controlled diabetic subjects who were restudied after intensive treatment, the same loss of glucose counterregulation was observed. This demonstrates that there is an *acquired* defect in epinephrine response that results from treatment. **The diminished epinephrine response is induced by episodes of antecedent hypoglycemia, and studies have shown that scrupulous prevention of hypoglycemia can restore hypoglycemia awareness.**

The mechanisms used by the brain to detect hypoglycemia are not well understood. According to Tamborlane, there are three potential mechanisms for hypoglycemia-associated adrenergic failure: altered central nervous system regulation of the HPA axis, increased brain glucose transport, and alterations in brain-glucose sensing. Each of these potential mechanisms is supported by experimental evidence. In a nighttime euglycemic clamp study in diabetic children, there was no plasma epinephrine response to hypoglycemia during sleep, but there was an epinephrine response in these same children while they were awake.

It is still unknown whether frequent hypoglycemic episodes lead to impaired cognitive function. This question is difficult because there is no simple test to quantify the amount and degree of hypoglycemic exposure in patients, and there is no simple way to separate the potential adverse effects of hyper- and hypo-glycemia on the developing brain.

Hyperglycemia and Diabetic Complications
Michael Brownlee, M.D. (Albert Einstein College of Medicine)

Dr. Brownlee has had type 1 diabetes for most of his life, beginning at a time when there was no A1C testing, no way to measure blood glucose levels, and no insulin protocols that involved more than one to two injections per day. At this time pediatricians did not think that hyperglycemia could cause diabetic complications. He commented, "A1C is not the whole thing. With regard to hyperglycemic damage, I think that is an understatement."

Diabetes is still the leading cause of blindness, although the proportion of diabetic patients who develop blindness has dramatically improved over the years. When Dr. Brownlee was in medical school, about 60% of type 1 diabetic patients became legally blind. Now, that number has been reduced to about 4%. Still, renal failure, cardiovascular disease, and neuropathy (the leading cause of non-traumatic lower extremity amputations) are major problems associated with diabetes. Dr. Brownlee addressed three main questions during his presentation:

1) How does hyperglycemia cause microvascular damage?
2) How does diabetes cause macrovascular damage?
3) What is the mechanism underlying hyperglycemic memory?

The risk of microvascular complications increases as A1C increases, and there are several possible mechanisms for how hyperglycemia causes microvascular damage: genetic factors that determine individual susceptibility to damage from hyperglycemia, repeated acute changes in cellular metabolism and cumulative long-term changes in stable macromolecules that lead to diabetic tissue damage, independent accelerating factors such as hypertension and hyperlipidemia, and independent mechanisms of hyperglycemia-induced tissue damage such as increased polyol pathway flux. According to Dr. Brownlee, the four independent mechanisms that have been discovered for hyperglycemia-induced microvascular damage lack an apparent common element, and clinical trials in this area have been disappointing. Brownlee hypothesizes that a common upstream event explains how hyperglycemia damages tissue.

It is known that hyperglycemia does not damage every tissue in the body. **Cells that are not damaged by hyperglycemia are able to close the cell membrane gate that prevents excess glucose from entering, while cells damaged by hyperglycemia (such as endothelial cells) cannot slow the entering of glucose.** When the blood glucose level increases, the glucose level inside endothelial cells increases. The high glucose level in these cells increases the production of intracellular reactive oxygen species (ROS), and this production primarily happens through mitochondrial overproduction of superoxide by the electron transport chain. Hyperglycemia-induced mitochondrial overproduction of ROS activates all of the major pathways of diabetic cellular damage.

Diabetes also increases the risk of macrovascular damage, and Dr. Brownlee explained this process. Clinicians and researchers used to say that atherosclerosis in type 1 diabetes does not exist, but they were wrong. In a 2002 study by Larsen J, et al. (Diabetes 51: 2637. 2002), the number of type 1 diabetic patients with normal vessels was 0%! All 29 subjects had atherosclerotic plaques, and the average age of these subjects was only 42 years. Thirty-five percent of the subjects had <20% vessel area stenosis, 30% had 20-40% vessel area stenosis, and 35% had >40% vessel area stenosis. Brownlee clarified that hyperglycemia is not the major determinant of diabetic macrovascular disease; rather, hyperglycemia-induced insulin resistance in type 1 diabetes is the major determinant. Hyperglycemia-induced insulin resistance causes an increased release of free fatty acids (FFAs), which causes arterial disease because FFAs have a role in the overproduction of ROS in endothelial cells. *Brownlee emphasized that insulin resistance is not just a type 2 diabetes issue—it is a type 1 issue as well.*

Based on his unpublished data, Dr. Brownlee hypothesizes that prostacyclin synthetase (PS), a major anti-atherosclerotic enzyme, is involved in the mechanism underlying hyperglycemic memory. Dr. Brownlee showed photographs comparing a blood vessel from a normal mouse with a blood vessel form a mouse with without the PS gene. The normal mouse had a clear blood vessel, while the mouse without the PS gene had a huge arterial plaque, which Dr. Brownlee said was similar to the vessels of diabetic individuals due to PS. In a glucose clamp procedure, when non-diabetic subjects experienced a blood glucose level of 180 mg/dl for three hours, 90% of prostacyclin synthetase activity was inhibited, and after four hours, PS activity was shut off altogether. Twenty-four hours after having a blood glucose level of 180 mg/dl—long after the patients had gone home—there was still no recovery of the PS enzyme activity. Since most patients with diabetes probably experience blood glucose levels of at least 180 mg/dl every day, this effectively means that in most patients with diabetes, the activity of prostacyclin synthetase, a vital enzyme, is turned off all the time.

At the end of his presentation, Dr. Brownlee discussed how closing the loop will affect the link between diabetes and microvascular and macrovascular diseases. A study by Van den Berghe, et al. (NEJM 345: 1359, 2001) showed that intensive insulin therapy greatly reduced morbidity and mortality among critically ill ICU patients. Patients admitted to an ICU were randomized to receive intensive insulin therapy (maintenance of glucose level 80-110 mg/dl) or conventional insulin therapy (maintenance of glucose level 180-200 mg/dl). Those on intensive insulin therapy with a mean blood glucose level of 90

mg/dl had half the mortality rate of patients on conventional insulin therapy with a mean blood glucose level of 165 mg/dl. Brownlee pointed out that a blood glucose level of 165 mg/dl is not even that high compared to what is generally seen in U.S. clinics and hospitals.

In closing, Dr. Brownlee said that we currently have the tools to reduce microvascular complications by two-thirds, without even achieving a closed loop. Dr. Irl Hirsch made Dr. Brownlee aware of an amazing finding: in DCCT, patients on conventional treatment had a mean A1C of 9% and ~22% risk of retinopathy, while patients on intensive treatment with same mean A1C of 9% had only 8% risk of retinopathy. Thus, intensive therapy reduced the risk of retinopathy by 2/3 without changing the A1C level. Drawing on this finding, Dr. Brownlee raised the question of whether glycemic variability is an independent risk factor for microvascular disease.

What Is the Perfect Artificial Pancreas?: Nature's Specifications
Richard Bergman, M.D. (Keck School of Medicine, University of Southern California)

Dr. Bergman offered what he termed a "physiologist's perspective" on diabetes, beginning with a discussion of the complexity of the factors involved in the regulation of blood glucose: the liver, the pancreas, meals, incretins, insulin, free fatty acids, fat, and others. In addition to increasing glucose uptake by muscles, beta cells also decrease the output of glucose by the liver. In a non-diabetic person, there is more than glucose and insulin. Incretins (including GIP, GLP-1, and other peptides) are critical, and free fatty acids are an important signal to insulin secretion. Amino acids also stimulate insulin secretion. The CNS also plays a role in glucose regulation, and we know very little about this. Dr. Bergman stressed that in the long run, we are going to want to incorporate more than simple glucose sensing.

Many people are currently studying the underlying mechanisms that account for biphasic insulin secretion. First phase insulin secretion is very important because it takes a long time for insulin to move from plasma into the interstitial fluid. Insulin crosses the endothelial barrier to move from the capillary to the interstitial fluid. When a meal is eaten rapidly, insulin release spikes and then drops, resulting in an insulin level in the interstitial fluid that goes up rapidly and then levels off. Without this first phase secretion, glucose disposal goes slowly. **Dr. Bergman emphasized that the biphasic nature of insulin secretion will need to be incorporated into regulation in an artificial pancreas.**

Beta cells are "adaptive" in both the short- and long-term. There is a chronic adaptation to insulin resistance. For instance, in pregnancy, beta cell secretion increases as insulin sensitivity declines with the progression of the pregnancy. There is an increase in beta cell mass when insulin resistance occurs. Dr. Bergman stated that glucose is not the stimulus; the mechanism of this increase is currently unknown. Beta cell secretion times insulin sensitivity forms a constant that is known as the disposition index (DI). People with type 2 diabetes have a lower disposition index. **Measuring the disposition index is the most powerful predictor of who will get type 2 diabetes.** An increase in fat in a diet without an increase in overall calories leads to insulin resistance and reduced clearance of insulin by the liver, which normally clears 50% of insulin.

Dr. Bergman stated that the signal for beta-cell compensation for insulin resistance was most likely free fatty acids. He hypothesized that free fatty acids are the feedback signal that cause insulin secretion in response. There is a reduction in the amount of insulin degraded by the liver when someone becomes insulin resistant. Thus, the adaptive response of the body in response to insulin resistance is not only the secreting of more insulin, but also degrading less insulin. Incretins are also important to regulate blood glucose. GLP-1 is a hormone that comes from the same gene as glucagon and is secreted by the L-cells of the gut. It enhances glucose tolerance and has a short half-life. It has a glycemia-lowering effect that is independent of insulin. Dr. Bergman mentioned Byetta as a GLP-1 agent that increases glucose tolerance

and may increase beta cell mass. **Dr. Bergman said that GLP-1 may be as important as insulin in regulating blood glucose in non-diabetic individuals.**

With our current methods of insulin administration, in which we place insulin into the periphery, we must cause peripheral hyperinsulinemia. To create an artificial pancreas, it may make sense to use nature's beta cells as a model. Attributes of natural beta cells are that they have adaptation (acute and chronic), intraportal release, and feed forward mechanisms (incretins). One answer to this is adaptive control. **The long-term goal for improved feedback would be to use an insulin sensor, a free fatty acid sensor, and an integrating algorithm to estimate glucose clearance. Measuring glucose alone will not be sufficient; we ultimately need a "multi-layer" closed loop.**

There is evidence that increased 24-hour exposure to glucose enhances the aging process. Limiting exposure to glucose in monkeys alleviates signs of aging. Benefits of food restriction in monkeys include a decrease in oxidative stress and damage, a decrease in glycation, decrease in body temperature, better glucoregulation, a lower incidence of diabetes and osteoarthritis, and an improved risk profile for CVD.

The Fast Track To Make the Artificial Pancreas a Reality for Children with T1DM
William Tamborlane, M.D. (Yale University)

Dr. Tamborlane took a practical look at diabetes and the closed-loop system, articulating the need for an artificial pancreas. **He noted that the present methods of diabetes treatment improve but do not normalize blood glucose levels in type 1 patients and that the burden of care is extremely high.** Dr. Tamborlane advocated for a step-wise approach to a perfect system.

Options for insulin delivery include external or implanted and subcutaneous, intraperitoneal, or intravascular. The advantage of external insulin delivery is that we have decades of experience with the technology, and that it is now used by a large number of youths with type 1. Recent advances in CSII include dose calculators, wireless link to meters, and basal and bolus increments as low as 0.025 units. The benefit of using CSII in infants and toddlers is that it reduces severe hypoglycemia from 80 per 100 per patient years to 39 per 100 patient years. Disadvantages of the implanted pump are that it requires a surgical procedure and has a complicated refill protocol. There can also be pump failure. There is very limited pediatric experience, as there has only been one teenager ever to attempt an implanted pump. Dr. Tamborlane stated that there is very weak evidence that intraperitoneal is an improvement over a subcutaneous route of infusion.

Glucose sensors can be external or internal/intravascular, and they can be minimally invasive or non-invasive as well as chemical or optical. Dr. Tamborlane described the CGMS, noting that it is not a real-time device but rather provides a retrospective review. It has accuracy problems, particularly in the low range. Limitations of the CGMS included skin irritation; it can also be affected by sweat and motion, and children did not accept the device. In the Guardian RT and the Navigator, there is wireless real-time CGM. The next version of the Guardian RT will communicate to Paradigm pumps and eliminate the need for a hand-held display. On the implantable front, Minimed's long-term sensor is inserted into a central vein leading to the heart, and sensor replacement requires a surgical procedure.

DirecNet (Diabetes Research in Children Network) includes five clinical centers, with one coordinating center and one central lab. There are 91 children included, with a breakdown of about a third each in the age ranges of 3-7, 7-12, and 12-18. Dr. Tamborlane is the Chair of the Steering Committee.

We need effective algorithms to vary insulin delivery. A good algorithm would provide insulin proportional to the glucose level and have a slowly adaptive basal release. There is now testing of the combination of the Medtronic Minimed pump and the Guardian RT in a model where glucose scores

beam to a computer. In testing of a closed loop in children, there was good overnight control, but not perfect control, with problems especially in post-prandial excursions after breakfast.

Dr. Tamborlane emphasized that we cannot leap from bad control to perfect control. In 50 patients with a 7.5 average A1C, 50% of the post-prandial values were over 300 mg/dL after every meal. A closed loop system that has post-prandial values in the 200s is in fact a substantial improvement. Overnight control has not been a problem. **Dr. Tamborlane identified some lessons that had been learned so far: 1) there are exaggerated post-meal excursions; 2) there is excellent overnight control but lingering concerns about sensor accuracy.** As a solution, he suggested a hybrid, semi-automatic control with "priming" or conventional pre-meal blousing to cover most of the carbohydrate in a meal. He suggested setting a slightly higher than normal target glucose value (e.g., 120 rather than 90) to avoid nocturnal hypoglycemia. He stated that a hybrid open/closed system should be the first step, and he concluded by saying, "It is a complicated disease…diabetes is a humbling disease."

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NEW ENGLAND JOURNAL OF MEDICINE EDIC REVIEW - *continued from page 16*

The Diabetes Control and Complications Trial (DCCT) and its long-term follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, demonstrated that intensive diabetes therapy aimed at achieving normoglycemia reduces the risk of microvascular complications of type 1 diabetes such as retinopathy, nephropathy, and neuropathy. Moreover, the DCCT/EDIC study confirmed the causal role of hyperglycemia in the development of such microvascular complications.

The DCCT did not prove that tight control would reduce macrovascular risk, and the EDIC findings on the impact of tight glycemic control on cardiovascular risk have been long awaited. It is well known that cardiovascular disease (CVD) is more prevalent among patients with diabetes (type 1 or type 2) than among non-diabetic patients, and that type 1 diabetes presents at least a 10-fold increase in CVD risk compared to an age-matched non-diabetic population. Many researchers have hypothesized that there is an association between hyperglycemia and CVD, but clinical trials of diabetic patients have not demonstrated that long-term intensive diabetes therapy reduces the incidence of CVD. In the DCCT, there were fewer CVD events in the intensive-treatment group than in the conventional-treatment group, but there was not enough statistical power to conclude whether intensive diabetes therapy affected the risk of CVD. The DCCT researchers thus used long-term follow-up data on the DCCT/EDIC cohort to determine whether intensive diabetes therapy reduces the long-term incidence of CVD among type 1 diabetic patients.

EDIC data background: The DCCT randomly assigned 1,441 type 1 diabetic patients, 13 to 40 years of age, to intensive or conventional therapy for a mean of 6.5 years between 1983 and 1993. 1,422 patients completed the DCCT, and of the survivors, 1,394 (97% of the original cohort) consented to enter the long-term EDIC follow-up study in 1994. Patients with a history of CVD, hypertension, or hypercholesterolemia were excluded from participating in the DCCT study. 93% of the original cohort remained in the EDIC follow-up study through February 1, 2005, and in this *NEJM* article the authors report on the data obtained from this EDIC follow-up study.

As a reminder, intensive therapy in the DCCT consisted of at least three insulin injections per day or treatment with an external insulin pump, using at least four self-monitored glucose measurements per day to determine adjustments of insulin doses. The daily glucose goals in the intensive therapy group were 70-120 mg/dl before meals and <180 mg/dl after meals. The A1C goal was <6.05%. The conventional therapy group used 1-2 daily insulin injections, and there were no glucose goals in this group besides those needed to prevent symptoms of hyper- and hypoglycemia. The A1C

difference between the intensive and conventional therapy groups at the end of the mean 6.5 years of the DCCT was ~2% (7.4% in the intensive-treatment group vs. 9.1% in the conventional-treatment group, P<0.01). At the end of the DCCT, the group on conventional therapy was offered intensive treatment, and all participants returned to their own health providers. Differences in treatment disappeared and there was only a small, non-significant difference between the groups in the proportion of patients using three or more daily insulin injections or an insulin pump. Mean A1C differences between the intensive-therapy and conventional-therapy groups also disappeared over the 11 years of the EDIC study (8.0±1.2% and 8.2±1.2%, respectively; P=0.03). During the EDIC follow-up study, A1C levels were measured annually and fasting lipid levels and renal function were measured in alternate years.

At baseline, no patients in the DCCT had hypertension or hypercholesterolemia as defined by contemporary standards, and only 5% had microalbuminuria (urinary albumin excretion ≥40 mg per 24 hours). There were no significant differences in CVD risk factors at baseline between the intensive-treatment and conventional-treatment groups, except for a slightly higher systolic blood pressure in the conventional-treatment group. ***Notably, however, by the end of the DCCT, the two groups had very different CVD risk profiles.*** The prevalences of microalbuminuria and albuminuria were higher in the conventional-treatment group than in the intensive-treatment group (13% vs. 7%, P<0.01, and 3% vs. 1%, P<0.05, respectively). The mean A1C level was higher in the conventional-treatment group than in the intensive-treatment group (9.1±1.5% vs. 7.4±1.1%, P<0.01). By the end of the 11 years of the EDIC follow-up study, the prevalence of a serum creatinine value of ≥2mg/dl was higher in the group originally on conventional-treatment than in the group originally on intensive treatment (2% vs. 0%, P<0.05). The prevalences of microalbuminuria and albuminuria were also higher in the group originally on conventional treatment. However, the absolute difference in A1C between the two groups was only 0.1% at year 11 of the EDIC study (P=0.38).

EDIC data show far lower CVD in original intensively treated group. During the 17 years of DCCT/EDIC follow-up, there were 46 CVD events among 31 patients originally assigned to intensive-treatment, as compared with 98 CVD events among 52 patients originally assigned to conventional-treatment. The respective event rates were 0.38 and 0.80 per 100 patient-years (P=0.007). ***Intensive treatment, e.g., a 1-point drop in A1C, lowered the risk of any CVD event by 42%*** *(95% confidence interval [CI], 9 to 63%; P=0.02)* ***and lowered the risk of nonfatal myocardial infarction, stroke, or death from CVD by 57%*** *(95% CI, 12 to 79%; P=0.02).* A history of microalbuminuria or of albuminuria was significantly correlated with an increase in CVD risk by a factor of more than 2.5, and this in part explained the treatment-group effect. However, after adjusting for microalbuminuria and albuminuria, the difference in CVD incidence between groups was still significant. Between the groups there were no significant differences in the use of medications known to affect the risk of CVD, except for the use of beta-blockers.[5] Baseline characteristics that were associated with the development of CVD include the following: older age (31 vs. 27 years), longer duration of diabetes (7 vs. 6 years), presence of retinopathy, current smoking, higher BMI (24.0 vs. 23.3), higher total and low-density lipoprotein cholesterol levels (194 vs. 175 mg/dl and 127 vs. 109 mg/dl, respectively), higher A1C levels (9.5% vs. 9.0%), higher albumin excretion rate (19.3 vs. 15.7 mg per 24 hours), and assignment to the conventional treatment group.

The physiological mechanisms underlying the improvement in microvascular and macrovascular outcomes with intensive treatment and the prolonged effects of early intervention are not well understood. The authors cite several potential mechanisms mediating the benefits on CVD outcome. It is possible that the same glycemic mechanisms responsible for the reduction of microvascular disease

[5] Beta-blocker use was more common in the conventional-treatment group than in the intensive-treatment group at year 11 of the EDIC study (7% vs. 3%, P<0.05), which if anything would have reduced the relative benefits of intensive therapy on the risk of CVD.

incidence also apply to the reduction of CVD risk. This hypothesis is supported by the observation that patients who had a cardiovascular event were more likely to have had retinopathy and a higher albumin excretion rate at baseline. The generation of advanced glycation end products, which are known to have a role in CVD, may be implicated in the long-term effect of hyperglycemia on microvascular disease. Another potential explanation is that the beneficial effect of intensive therapy on CVD risk is actually a result of the reduction in the incidence of microvascular disease. Supporting this idea, researchers have hypothesized in past articles that renal disease and autonomic neuropathy are CVD risk factors. More work is needed to understand the power of "metabolic memory" but at the very least, the piece certainly supports the notion of good control as early as possible.

There are four main limitations of this study, according to the authors. First, the total number of CVD events was too low to allow a definitive analysis of treatment effects on the risk of CVD events. Second, determination of CVD events is partially dependent on the clinicians' judgment and thus is subject to bias. A third limitation is that the intervention groups were unmasked during the DCCT and EDIC study, which establishes the possibility of bias in assessing CVD events and in selecting therapies that can affect the risk of CVD. Finally, there was a relatively high fraction of silent myocardial infarctions. In defending the relative lack of bias in their study, the authors note the uniform collection of historic data, the clinical severity of cardiovascular events, the masked determination of events, and the treatment of the DCCT/EDIC subjects predominantly by non-DCCT clinicians.

Overall, what matters? This study demonstrates that intensive diabetes therapy has long-term beneficial effects on the risk of CVD in type 1 diabetic patients and supports the original DCCT recommendation for intensive therapy to be implemented as early as possible in type 1 diabetic patients. The 57% reduction in the risk of nonfatal myocardial infarctions, stroke, and death from CVD with intensive therapy is greater than the reductions in risk achieved with antihypertensive medications, cholesterol-lowering medications, and other proven interventions.

Perhaps it is not a huge surprise that tight glycemic control benefits macrovascular health, but this study is momentous for actually proving it, and its quick publication – in NEJM – is encouraging. We hope these findings reinforce the importance of tight control and encourage diabetic patients to seek tighter control earlier and more intensively. This data are also important for payors, as the results lend further support to intensive therapy.

What's troubling, however, is that even after such historic studies as DCCT and UK Prospective Diabetes Study (UKPDS) have demonstrated the importance of good glycemic control, two-thirds of patients are still above the recommended A1C goal of 7%, and glycemic variability is high as well. We believe this is due at least in part to the fear of hypoglcyemia, as well as to the imperfect tools that patients must use. We think, however, that future drugs and therapies should make it easier to avoid glycemic variation while improving A1Cs generally. We are concerned, however, that even those that are "at target" may not be as healthy as they appear, because they may suffer from frequent hypo and hyperglycemia. We advocate that the risks of glycemic variability be addressed by all means possible.

The study raises the question for many as to whether it is possible to extend the results of EDIC to type 2 patients. ADA notes that type 2 diabetes increases one's cardiovascular risk two- to four-fold compared to someone who does not have diabetes.[6] The Centers for Disease Control and Prevention (CDC) have documented that in 2003, 28% of Americans with diabetes aged 35-64, 48% of Americans with diabetes aged 65-74 and nearly 60% of Americans with diabetes aged 75 years or older had cardiovascular disease.[7] While the EDIC findings are *directly* relevant to type 1 diabetes, we certainly

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

believe they may ultimately be shown to have implications for type 2 diabetes as well. We will look for similar extension studies to UKPDS and certainly at the very least, hope that interest in tight glycemic control and reaching A1C targets will continue to intensify.

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From Diabetes Close Up, many great wishes to you and yours for 2006!