DIABETES CLOSE UP

Diabetes Close Up
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Glycemic Variability: A Closer Look

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

From the Editor: Nothing stops – it is an(other) explosion of glycemic variability (GV)! It's been an incredibly exciting few weeks on the diabetes front and on GV in particular (defined as the instability of blood glucose, both hyperglycemia and hypoglycemia). This issue is a follow up to our December 2005 issue, "DCU on Glycemic Variability." We wouldn't be writing about it so *soon, but … it really is relevant to so many segments of diabetes and, it's excellent to see this theme on such a roll. Think about these related happenings over the last two months:*

- *Dex Com's continuous monitor STS is approved in March in record time;*
- *Medtronic's sensor-augmented pump is approved in April, six months ahead of expectations (real-time continuous monitors are all about reducing GV);*
- *JAMA publishes groundbreaking research on GV in mid-April by Dr. Louis Monnier (see our "Three Questions" piece later this issue along with this issue's lit review);*
- *JAMA publishes oh-so-prescient editorial by GV experts Drs. Michael Brownlee and Irl Hirsch (read about it also in our lit review, along with a review of Dr. Chris Saudek's take on A1c);*
- *Dr. Hirsch gives an excellent talk at the Mannkind investor day in April, where he emphasizes that that glycemic variability is pro-inflammatory (that's bad- an insulin that decreases GV will help patients reduce inflammation). He says that more focus on post-prandial glucose is needed and all therapeutic strategies should be evaluated for how they lower GV and A1C ("the FDA looks at A1C and fasting glucose—that is not what is fueling complications," he stresses).*
- *Dr. David Klonoff's Clinical Diabetes Meeting in Boston in late April has multiple GV sessions - crowds scribble as they learn about "Oxidative Stress 101" – again from Dr. Irl Hirsch;*
- *AACE is <u>full</u> of other GV references, from exhibit floor to plenary sessions to symposia. One of the most interesting posters at AACE is "Exenatide and Glargine Differentially Affect Postprandial Glucose Excursions in Patients with Type 2 Diabetes" – this remarkable analysis suggests that, regardless of endpoint (A1C was the same for both), exenatide improved hyperglycemia by reducing both PPG excursions and fasting glucose, while glargine reduced fasting glucose only. Our read: all A1Cs aren't equal because a causal relationship between PPG excursions and macrovascular complications has been suggested (or, Byetta is better).*

So we remember a number of times over the past few years where there was a <u>little</u> attention on post-prandial – then none – then a tiny bit more attention. Now, plenty. The next step is to build further evidence to prove decisively that GV matters. When that happens – and it seems, now, when, not if – reimbursement may well improve. (Okay, call a spade a spade – you can't improve from zero – what we mean is, reimbursement may well happen. Let's lobby, for reimbursement for devices, drugs, AND healthcare professionals' time). Yes, there is momentum behind this measure in a big way and, we're very excited to see so many strides in 2006. Read on in this issue….

So we love meeting famous people – can you imagine how delighted we were that Professor Marion Nestle accepted our invitation to dinner last week? Hard core, smart as a whip, and oh-so-together. We have learned so much from her new book What to Eat (yes. really.) and we recommend – if there is ONE thing you do Tuesday May 2– one! – everyone should run to their favorite independent bookshop and buy

it. Amazoners out there, you should know, the book is already #175 (#300 or better on the buried sales number means you're selling at least 100 or so books a week) - please point your browser to here to see Marion's top ten books on food (wow is mostly and you should pre-order or order What To Eat http://www.amazon.com/exec/obidos/tg/guides/guide-display/-/33MYLRLDB403Q/sr=53-1/sr=53-1/qid=1146215549/ref=tr_295641/102-5410329-5576911! So exciting! Another brilliant, recently published book, Syndrome W, by Dr. Harriette Mogul, teaches us so much about pre-diabetes, why insulin, not just glucose levels, are key to check (yes, probably most of us), and most importantly, how to do something about it. Reviews coming on both books post ADA.

In other news – to close out the month, Sanofi's rimonabant received approval late this month from the EU and it will be very interesting to see what happens here in the US, as the press release was more or less written as a plea to the FDA in our mind, especially quote about how we should really downplay cosmetic applications. The last release, about the FDA approvable letter, did not have the name Acomplia in it (at all!) but the name is now back on this release. In the EU, as in the US, the drug received a non-approval for smoking cessation.

DCU's Next Phase

Our thanks to all who filled out the reader survey – nearly 100 of you! You gave us highest marks for our assessments of conferences and companies, and you also loved the speed of our blog, our patient-focused eyes, and our network of industry leaders (on that front, see our interview in this issue with Davida Kruger). You told us something else: you want more information, more quickly, more often. As the diabetes world has expanded – in new products, promising research, and, of course, actual patients – Close Concerns has tried to expand with it. We've added staff, increased our conference coverage, and upgraded our website. We've now logged nearly 60 newsletters in almost four years, we write a blog entry or two every week, and we're at key meetings every month (the last weekend in March alone, for example, we covered meetings in England, Amsterdam, and the US). We continue to increase our knowledge of the industry, and we have built relationships with the most important figures in the field. We believe we deliver essential information to anyone interested in the intersection of commerce and diabetes, and we're gratified that our recent survey confirmed our views.

Based on your feedback, we are further increasing and intensifying our focus on the field. As you might imagine, for us to maintain and increase our commitment – to increase our coverage and to travel around the country and the world to give you the latest, most accurate and most important information – we can no longer provide DCU for free. As the field has grown, we simply need more resources to grow with it.

So beginning next issue with our ADA preview and AACE postview, Diabetes Close Up will be available by subscription only. We are grateful for your readership and hope that you will look forward to this exciting new phase of DCU. Please visit our website at www.closeconcerns.com, where you can find out how to subscribe. We promise to maintain and exceed the standards that DCU has already achieved – and to ensure that it's the leading source of information on the business of diabetes. Really, we feel like we're just getting started and we couldn't be more excited.

--by Kelly L. Close

In this issue:

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.

- **April 28: AACE – "Like being on acid…"**
- **April 20: DexCom accuracy figures published in AACE abstracts – wow!**
- **April 16: EXCELLENT day for Medtronic! Sensor augmented pump approved ~ quickly!**
- **April 11: JAMA bolsters glycemic variability**
- **April 10: AP article draws attention to hospital care for obesity**
- **April 2: Diabetes hits the mainstream again – Byetta in the comics!**
- **March 29: Diabetes fails to impede Adam Morrison's path to stardom**
- **March 27: DXCM STS approval – click, click, click –**
- **March 26: Amylin LAR – What isn't being said**
- **March 16: Symlin, a year in! CC on the NYT on Byetta**
- **March 14: Alice Waters speaks out about preventing childhood obesity**
- **March 8: Revised obesity projections darken picture of (near) future**
- **March 8: Dr. Irl Hirsch on the value of glucose monitoring**
- **March 1: NEJM piece addresses A1C reporting in NYC**

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

1. DexCom STS comes to market: A personal take

The FDA's recent approval of the DexCom STS has brought to market the second continuous glucose monitor. Since the first one is available mostly in conservative cities in Texas, I decided I would wait for a bit. In my past professional (Wall Street equity research) and personal (patient) experience, approvals never happen on time, so I was delighted when an East Coast diabetes watcher blackberried me early one morning that Dex Com had approval – I was so excited! This was definitely a bit earlier than expected, though 12 months after the company had submitted. Clockwork! Dex Com seems to achieve most other milestones it sets for itself, so it shouldn't have come as a surprise. Nice! True to the company's word, it shipped the first devices the week after approval. I have been asked a lot recently what training was like – easy. I was trained the same day as my doctor and two other (what we call) hyperintensively managed patients. We were all trained in 30 minutes. It's easy and intuitive, and there's not too much to screw up. It will become slightly more complex with software, which the system doesn't yet have. Although I viewed this as a real downside on day one, the system helps so much throughout the day that I've done a 180 and nearly decided the software isn't necessary. Of course the software will be wonderful and I wouldn't miss it for a second – but having the score and trend right on the device that shows 1 hour, 3 hour and 9 hour trends – you've got most of what you need to get through the day. So I'm thrilled the launch wasn't delayed for software.

The company is running fast, the launch is fast and while everything isn't in place, the company has made some very strategic decisions on important pieces to hit on – size of transmitter and ease of use are two aspects of the product that are very well done. It will be up to doctors and educators to determine what patient segments can use the device easily and safely, but beyond that, I imagine the demand coming from patients directly will be high, and will get really high once reimbursement emerges. Until then, asuming they can pay for it, for certain segments of patients, 24/7 real-time glucose monitoring makes complete sense: 1) hyper-intensively managed patients (patients checking 6-8+ times/day); 2) intense athletes (for a really excellent patient blog on this, check out Matt Vogel's insulinfactor.com); 3) anyone on Symlin; 4) pregnant patients; 5) patients who want to get pregnant (getting to an A1C under 6 isn't that easy but this will help enormously); and 6) anyone with problems relating to hypoglycemia, hypoglycemia unawareness, nocturnal hypoglycemia, and gastroparesis. And on it goes. While other groups can and will certainly benefit (truly, I think *any* type 1 patient, and *any* type 2 who wants to assess how their therapy is working or who isn't at their glycemic goal), these are the first that come to mind for me, having experienced all the benefits for a couple of weeks.

So after two weeks on the STS, my overall impression is very positive, except for cost (~$14/day, all in). There has been surprisingly less hassle factor than I had anticipated. A word on reimbursement - the STS certainly has major clinical benefits, particularly in alerting users to hypoglycemia, in spotting early and crushing post-prandial hyperglycemia, and in signaling basic glucose trends. But the funny thing? I'm not sure CMS is going to give any credit for signaling trends. As we know, it's all about producing evidence and getting it published, and we salute *everyone* working on this front. Although STS doesn't yet have a replacement for traditional glucose monitoring, that doesn't seem to be what concerns patients, at least the ones I know who are lucky enough to have a device like this. For me, trend trumps accuracy nearly every time. My *first* day, I checked my blood glucose often, to see how far off it was. Pretty consistently, it was about 20 mg/dL off. Higher, at higher levels, and occasionally very off. Once it was 100 mg/dL off – it would be better if that hadn't happened and it would be better if there were no accuracy/clinical utility tradeoffs. That'll be the "best in product" product, and it could come from any of the top three – Abbott, Dex Com, Medtronic – and when we have that choice, life will be even grander! But now is now, and this is what we have, and it's amazing to me how much this has changed me! It's quite breakthrough. Very

often, the STS is right on the money. Other times, as I said, it isn't, and I sort of figure out directionally where it is headed … it's iterative, for sure. But so incredibly useful.

Back on reimbursement for a second - it is unsettling that there seems to be so much focus on replacement in order to get reimbursement – it's like a manta gone wrong. Remember, even the label for a "traditional" monitor doesn't allow it to dose for insulin – rather than wait for a panel of experts says it is all right for these devices to be used for dosing decisions (and why, really, in the Vioxx era, in this litigious environment, do we think doctors would say that anyway?), proving how much money is saved from less hypoglycemia and DKA prompting hospital visits seems like excellent work to be doing. As a patient, I'm certainly grateful for this. Dr. Lori Laffel at Dr. Klonoff's fantastic meeting on continuous in April pointed out that $2.5 billion per year is spent on DKA alone. So if every episode costs $2,500, that means there are 1 million of these episodes per year. That is crazy. There is zero reason that any diabetic needs to wake up, paramedics gleaming in their eyes, talking about hypos – and there is zero reason anyone needs to experience DKA. Both are miserable and both are incredibly, incredibly preventable using tools like STS.

Back to the product. While several aspects of the STS await improvement (software – they need it; better readings the first day – they need them; the calibration cable – lose it), they did, as noted, get some critical things right. It's little! Many patients *so* care about this. On-body real estate is a big deal for kids and women in particular. (This isn't approved for children, by the way, but that must be just a matter of time; if I had a child with diabetes I would be counting the days ….) It's simple. It's easy to teach, easy to learn. It's hard to screw it up and it's hard not to derive clinical value from it. It's hard, actually, not to become addicted, for yours truly, who admittedly, if anyone would be come addicted ...

The most important is reimbursement. Given the high cost of the system, success of the product will hinge on reimbursement. This will be vital for the STS – and/or any other continuous monitoring system – to make a significant dent in the market. But, I shake my head – it's this good – how could reimbursement not happen? Naïve, I'm sure.

Back to the start. As I was telling you, two Wednesdays ago, a DexCom representative spent half an hour teaching me to use the STS, which consists of a receiver (smaller than most insulin pumps), a transmitter, a sensor, a cord, and an applicator. The training was not complicated; in fact, the system itself isn't that complicated, with relatively few bells and whistles (that's good in terms of economics for everyone– easy, basic). This should increase acceptance among doctors who don't want to spend a lot of time training but may disappoint some very intense (read: cool) HCPs who want to pore over 7-day tracings, etc. I wish I wanted that, but I don't, right now – I just basically love using the device on a much more basic level – smoothing out swings pretty often, for example. How often, you ask? Kind of all the time. Just little blips here and there – but I'm convinced this will result in better short- and long-term health.

Using the "applicator," I learned to insert a sensor in my abdomen, which was relatively painless. It is not as painless as my Insulet pump, but it's not as painful as blood glucose monitoring – that is, episodic blood glucose monitoring. And it is one million times less painful than a traditional pump introducer needle.

The transmitter fits snugly above the sensor on my stomach, from where it signals glucose levels to the receiver. I waited for the two-hour calibration time, which expired when I was in the middle of dinner. The receiver is calibrated with a LifeScan Ultra meter (I happen to find four in drawers in my house – I loved this meter when it came out), so I used such a meter to check my blood sugar (twice), then connected the meter to the receiver with a cord. The meter read 190. The receiver read 205. I was off and running. WOW! I was way too high even though a couple hours earlier I was 82 – that's the point. My whole life has changed. Go to "correct" and remember – maybe I have insulin on board. Indeed! I had

been to Noah's for a bagel 90 minutes earlier and yes, I could see that right on the display! (More or less – not, of course, that I could see anything but a trend – but I could see exactly where the carbs started pouring into my blood stream. Yes, this does have the power to chainge behavior)

I kept clicking the button as time passed – I was now at Quince, my favorite restaurant in SF, with a friend who was eating with me and watching out, since John was traveling. "Here's my one hour trend," I kept showing him. "Here's my three hour trend." Pause, beat, beat. "Here's headed toward 9 hours – we are only two hours in, but check it out!" I liked STS so much, I was sort of boasting for it about its achievements. This is insane, I know – but it's an insane life.

I was initially pressing the button to see my glucose level about every half hour, and later, I even woke up several times at night to check. I must say, it was so, so, well – so gratifying. I felt safe, and I felt like I had come home.

I realized, when you get down to it, continuous monitoring helps me feel more normal. That's rare, and special. With diabetes, it's hard not to always feel this same sort of dispiriting background kind of anxiety. I'm so used to it I don't even ever think about it so actively and those of you who know me know I can tell you one zillion things that are positive about research in the diabetes field, but day-to-day, hour-to-hour, minute-to-minute I never *really* know what's going to happen next to me and there's always a sense that either my numbers are probably wrong or will probably be wrong shortly or could be wrong in two hours – the STS just tells you.

It's the most excellent connect-the-dots game I've ever played.

More on trends. I was particularly interested, on the trends, in the "direction" of the dots, indicating whether my glucose level was increasing or decreasing. As noted, three different screens give you trend lines over the past nine hours, three hours, and one hour. These trend lines are probably the most valuable part of the system. You can set the receiver to alert you when glucose readings hit certain levels – I set mine for 60 and 160 – but you still need to check your blood sugar conventionally before you take any corrective actions. Theoretically, I guess there are accuracy issues and lag issues – but when I'm wearing STS and I get the direction I'm headed – that's really all I need to know.

Now, with Navigator, apparently one gets *projected* alarms. I like that idea, since it means I can avoid hypo- and hyperglycemia, not just deal with it. I'm on board with the STS right now since it is available – I wear an Omnipod, so I wouldn't personally dream of moving to the sensor augmented pump myself, but this excellent new world – it's not about my choice or your choice. What is exciting is there is LOTS of innovation happening and it's only going to get better, as long as Washington gets religion.

Back to the system. While the receiver itself is fairly small and sleek, the system has many parts: the receiver itself, the sensors, which must be replaced every three days; the applicator, and the cord, as well as the LifeScan meter and strips (if you don't use those already). Most patients have nightmare stories about losing one of their supplies – an insulin pen, the cartridge cap of an insulin pump, whatever – and these CGM systems will give us even more stuff to track (and lose). So far, I've left the transmitter at home on one trip, I've left the Ultra somewhere else, and in that case, I had put the cable in the Ultra case. It's comical. I've basically lost everything you could lose, two weeks in, and that's not great from a customer service perspective. Yet and still – like I noticed with my Omnipod, you leave it on one plane – you don't do it again.

So despite all my blaze of enthusiasm, yes the STS has clear limitations. Because it comes with no software, so you can't download and analyze glucose readings with your health care provider. They probably won't be so happy about that. But I assume that's temporary. There is no way to mark events

like insulin intake, food intake, and exercise, as you can now on many insulin pumps. I'm not sure where I am on that yet – it makes it simpler, so on one hand it isn't bad, but on the other hand, when there is software, that would be something nice. The receiver's horizontal axis doesn't have time labels, so it's hard to determine which BG trend corresponds to which time. The hypo/hyperglycemic warning is both vibration and sound – but it appears you can't turn off the sound, so you shouldn't bring the receiver into, say, a movie or anyplace quiet – or, just sit on the aisle. And then the whole accuracy thing, which I won't go through again, since I don't think it matters so much.

It always comes back to cost. The receiver has an introductory price of $500 but will be raised to $800 (it's unclear how long this promotion lasts, which is marketing 101, to pull people in) and the sensors are $35 each. You still have to buy test strips, though probably not as many (but at least four per day – calibration is twice daily with two strips). Those are significant expenses, affordable for some but not for many others. Many insurers will resist reimbursement, on the grounds that CGM is not essential to care; but my hope is that insurers, starting with Medicare, will recognize the clinical benefit in all continuous monitors, particularly in pre-empting serious (and often costly) hypoglycemic episodes. Thank you again for all the studies being done to get and publish evidence on this front.

The STS is expensive for me, and my plan at the start was not to maintain it 24/7, but now there's no way I won't have full time use of it. Here's the test. I say to John, "*So the STS is $350/month. What do you think?"* John looks up, now settled on the couch, helping our one-year-old Coco bang out a tune on a tiny piano. "*$350/month?"* Audible sigh. "*Well, it's a no-brainer, isn't it*." They bang a little more. "*We're really lucky, you know*?" he says. "*We can afford this. Sort of, or maybe we can't, it feels very expensive. If you asked me if you thought you should spend an extra $350/month at Erica Tanov, or if you asked me if you should buy 25 more CDs a month, there's no question what my opinion would be. And yet and still, this feels cheap, given everything. You're safe. You're less worried. Coco will be safer. Coco will be safer! So I'll be safer and happier! I won't have to ask you to check your blood glucose anymore. It'll make me worry so much less when I'm not here."* Pause. *"It's our secret weapon, isn't it?"* Pause. *"Despite the noise and the battery power that needs to work longer and the accuracy issues ... Look at you. I can see – I can SEE – how much calm is it bringing into our lives. You love it. You're so proud of it. All patients deserve this, no? Look at you. I can touch how much calmer you are. You really do already love it."* Pause. "*It works for us, they did it right – a lot of it, anyway - we'll find a way to pay for it."* Pause. "*I've been waiting so long."* Pause. "*I know it's not about me, but ... it is."* Pause. "*The really awful about is that it is limited to people like us who can afford it.*" Pause. He's right. There couldn't be anything more sobering. Let's hope all of industry involved in this innovation can get the evidence and publish quickly and show what any intensively managed diabetic knows without a doubt – that John's right, that this is a no-brainer.

—by Kelly L. Close

2. Interview with Nurse Practitioner Powerhouse Davida Kruger

Diabetes thought leader Davida Kruger on reimbursement for education, inhaled insulin, Byetta, Symlin, continuous monitoring, and revolutionizing the standard of care

For the fourth interview in our series, we spoke with a certified nurse practitioner in diabetes, Davida Kruger of the Henry Ford Health System in Detroit. She shared with us her views on new drugs, new devices, and the future of diabetes therapy:

Kelly Close: Can we talk about the importance of patient education in light of all the new drugs right now?

Davida Kruger: Well, I think we have to make sure that we emphasize the importance of patient education with all of the medications and devices. We also don't want to steer people away because they think there is just too much to know. So I think there's a fine line. I think that if you look at the patient indicators from Amylin, for Symlin, they're very clear. Patients need to see an educator. Educators have the time and knowledge to help patients be successful. And so with a medication like Symlin, the patient is going to be much more successful if education is done. Byetta's not the same in terms of the teaching. Novolog Mix 70/30, which is a really revolutionary mixture if you think about how that drug works, is not an issue. I really think that it's prime time for people to utilize educators and understand the importance of education for patients to be successful. But even if you look at how easy it is to use Byetta, patients will benefit from education.

KC: So what are you hearing from patients who are using some of these new drugs and devices?

DK: On Symlin, it's the first time in their life they've ever been able to follow a meal plan because they're not hungry. So now we have to go back and provide an opportunity for patients to really learn the nutrition plan; whether it be Weight Watchers or ADA approved, whatever. It's the first time that they've had control of their food intake, so let's go back and provide the support and education in medical nutrition. Patients are thrilled with how flat their blood glucoses are after meals as well.

KC: Right .. right! I love Symlin. So this is fascinating - one of the things that we've heard, which is really different from any other drug that I've heard of, is that the outcomes in the field are actually better than they were in the clinical trials. Dr. Harold Lebovitz was the first one who said that and we continue to hear it.

DK: Yes, I would say that too. The outcome in the field is a hundred percent better.

KC: Wow – why do you think that is? What's happening that is different?

DK: I'm constantly saying we finally have a chance to take these drugs out for a real test drive, because when you have to hold to a the letter of a protocol in a clinical trial, you can't *be* your own clinician. [KC: What a drag.] You can be a safety guru to make sure that the patient is safe, and you can also make sure the protocol is followed to the letter of the law. But now I get to sit in front of the individual patient and see how Symlin or Byetta best fits into their life. And I'll tell you, the A1C lowering and the weight loss with both of these drugs are so much more dramatic than what we ever saw in clinical trial.

KC: So what are you seeing? Are you actually seeing A1C drops of more than a point or so, from a lowish baseline?

DK: Yes. Yes. Yes. In fact, what I'm seeing is so dramatic, and I know I'm not the only one, that I keep trying to send these case studies to Amylin saying these are better than what you're using for your training. And they keep saying we can't use them because we have to stay within the guidelines. So, yes, I am seeing dramatic weight loss, and I am seeing *dramatic* lowering of A1Cs way beyond what the FDA approval was based on.

KC: Wow, okay. I think that's so interesting for people to hear. Can you talk about how patients feel about the drugs now that they've been out for a year?

DK: Oh yes. You know, there's always naysayers in the world, but I'll tell you that my patients do not turn away from three extra injections a day if they get the benefit of Symlin. Or people who are not on injections, if they have type 2 diabetes, do not mind taking the two injections if they get to use Byetta. It's a different thought process with Symlin. I am not minimizing the fact that there's a whole psychology to

taking injections. Please don't ever assume I'm minimizing that, Kelly. But we can lay out a benefit to a patient that their A1C will be lower, their blood glucoses will be better, and they probably will lose weight and feel better. I do not hang my hat on the weight loss part because there're going to be patients who aren't going to lose weight, and I don't want them to get discouraged from the improvement of the A1c and blood glucose lowering because for them that's still a *major* benefit, and that's not a reason not to use a drug. But I'll tell you, I don't have patients that turn away from using Symlin or Byetta because those drugs are injectables. I just don't.

KC: That's amazing … so switching gears, we want to ask you about DexCom because we saw the STS approval last week. Will continuous monitoring revolutionize diabetes care?

DK: Absolutely. Absolutely. The more data we have from patients, the more we can help them. Of course, nobody wants to be overwhelmed with a zillion, trillion blood glucose points that they have no clue what to do with. But the reality is, if you can give me blood glucoses ten times or twelve times a day, or whatever you can give me, the more you can give me, the more I can help you. Because I can do pattern management with those and help patients learn to do the same. If I could say to the patient, let's look at the data from your continuous glucose monitor, how much better is that for the patient not to have to poke their finger, but just to give me graphs or to give me the data that comes out of a device like that. I just think it's going to completely revolutionize diabetes.

DK: I think the other thing that you have to keep in mind is that diabetes is so much more complex than it was five or ten years ago with all the new drugs. So with the exception of Byetta, which you really don't have to step up your frequency of blood glucose monitoring, most of the other drugs on the market you do to get the most benefit. So the combination of Symlin with the sensor, or any of the other new things on the market with the sensor, has great potential.

KC: I'm going to move away from this for a second, although my next question may be related. I'm wondering, what are patients actually asking about these days? What do they come to you and ask about? What's switching them on, or off, or what are they getting, or not getting?

DK: You know, just like the healthcare professionals, a lot of them are confused about the difference between Symlin and Byetta. There are two recent articles to try to explain that. But they come in with an understanding—let me say, they have most recently started coming here with more and more questions because the drugs have been out for the market review now, and they're looking around at their friends, and they're looking at blogs and they're looking at all kinds of other stuff, and so the hype with these drugs with the patients now is just really starting; so that they're calling and saying '*My friend is on this drug, tell me about it.' 'My friend lost weight on it.' 'My friend's A1C is better on it.*' So now I think patient demand will be the next round in the rolling out of these drugs. And so the providers who have not gotten on board, and there's still a ton of providers who have not gotten on board with either of those drugs—

KC: Wait, wait, wait, what do you mean, not on board?

DK: There are endos and PCPs that are not on board with either drug, but they're getting pressure from their patients. I've seen my community where, you know, we've done all the research so we're on board. We've been on board since the day we could write a prescription. So now our patients are out there in the diabetes community, and you know how tight the diabetes community is as a support group and chatting with each other, so they're saying how come you can get it at Henry Ford hospital and we can't get it at 'x' hospital?

KC: Talk more about that. You mentioned blogs -- is that different from five years ago? From a couple of years ago?

DK: Well, I think it is. It doesn't matter what age you are, I think people are so quick to turn on computers and so literate about computers, that I think that you are definitely seeing more people who are picking things up online and asking questions. Those drugs, you know, have not been marketed direct to consumer, but I tell you, we get a lot of patients saying we want this drug.

KC: What's your take on direct to consumer marketing?

DK: I think that the consumer has the right to know everything about the disease that they live with and every aspect of it. While some of that direct to consumer is hype, why should the health professional be the only one to hold the information? Why shouldn't the patient have something that's direct to consumer that gives them the opportunity to then go online, learn more about the drug and ask their providers intelligent questions? Why should they have to depend on their provider to say to them, by the way, a year ago this new drug came out and it might be good for you? I mean, I still see docs that rush from oral to insulin because they aren't comfortable enough with Byetta. So why shouldn't the patient have the information and the understanding, say to the physician or the providers, can we look at Byetta first? Why should it be any different than me buying a TV? Why shouldn't I understand every one that's on the market? And this is more important. Why shouldn't you be an informed consumer about your diabetes care?

KC: We've talked about inhaled insulin in the past, what I'm wondering, is, if you were advising Pfizer on inhaled insulin—and maybe you are, they certainly would benefit!—how would you say that they should launch it?

DK: I think they should bring it to the specialist first. They want to help the specialist pick the right patients and be successful with the right patients. Then expand from there. I think that is the best way to bring it to market.

KC: So who do you think is the right patient?

DK: Well, I'm having a hard time with that. Because whoever takes it still is going to have to take long-acting insulin. And right now, every new product, every new drug, you always want the first generation because that's how you get to the second or third generation. So I applaud them for being the first ones out there. But I think in some instances, for some people, the device may be too bulky. So I guess it's for people who truly are bothered by injections, who want a different way to administer their insulin, are willing to take a bedtime injection, but during the day want the freedom from injection. I also think it has to be a fairly motivated patient, because there's a learning curve to it. It's not 'here's a pen, use it.' So you want to make sure—it's like Symlin, you have to have a motivated patient.

KC: Thinking about insulin makes me wonder - what kind of challenges do you see, just in terms of the whole adherence problem, patient adherence to drugs or to monitoring? Are emerging devices helpful?

DK: Well, I think what you have to remember is that life is really … *busy*. I think if you look at any of us – I have hypertension, I have lipids, I have all these other issues that I am personally dealing with. I understand what the ramifications are if I don't take care of them. Do I always eat well? And when I'm on the road, how do I compensate for all of that and how do I manage to get all of that done and still live my life? Then you think about people who have all those diseases I just mentioned, and they have diabetes. That's typical. So I'm saying to you, I want you to exercise. I want you to follow a diet. I want you to take six blood glucoses a day. I want you to wear an insulin pump. I want you to take Symlin and I want

you to call me every three days. So, tell me, Kelly, would you have time to have a life? So is the issue adherence or life?

KC: Right. Hmm. Right. How I wish I had a rejoinder … but of course, I don't.

DK: I think it's really difficult. It's not an issue of adherence for the patient. It's that there is just so much that needs to be done to take care of diabetes, and we have to ask patients to *do* so much. How do we make it reasonable for the patient? Because I think what I'm offering is a way to prevent complications and improve outcomes for the patient, but am I going to make your life so complex that that may not be what you want. And I don't mean that in a negative way; it's not adherence; it's the fact that we all have incredibly busy lives and how do I help a person with diabetes incorporate as much as possible to have the best outcome?

KC: Right. Yes. I actually think, having been on the STS for five days, it's just amazing to me. I was a little worried about just too much information, but it's just amazing. It's like you're just giving me the *right* information. Even if it's wrong – I can fix it. You're giving me a way to feel better in an easier way. And you kind of said the same thing with Byetta, right? This is so interesting to me.

DK: Getting back to where we started, I really think the key is education, and I really think the key is support systems. And I need to put this into my practice when we put you on those drugs, you have 24/7 access to our care. So that means you're emailing us, you're calling us. You can reach us so that you're successful.

KC: Right. Your patients are so lucky! I wish that could be possible everywhere. The last questions I had were around like the DPP-4s and other new drugs coming out. What do you think about those? What will be most important five years from now? What if the data show regeneration? Is that likely? Can we talk a little bit about how you think about these new therapies?

DK: I think there's going to be plenty of places for all these new therapies. I think that we're going to continue to learn more and more and more. I think that we have underestimated the potential for Symlin and Byetta in the community and what they can do. I think that that's not a bad thing. I think now that we have it in our hands, we know how good they are, we just need to apply them in different ways. And I think all of those drugs are going to have their overall niches in the world. I look at Novolog Mix 70/30 and I think, who would've used a mix? But I like Novolog Mix 70/30 because you can use it three times a day and you can get a patient down to 6.5 if you put them on three times a day. I like to add Symlin to it. People come down from A1Cs of 10 percent with the combination of Novolog Mix 70/30 down to an A1C of 6.5 percent, and they don't gain weight if I put Symlin on.

KC: Would you put them on Byetta? Why do you choose Symlin? Or is it dependent on the patient?

DK: It depends on the patient. Of course, in a couple of my patients there was a reason why it had to be Symlin—

KC: They were already on insulin?

DK: Both those patients were already on insulin, and their A1Cs were too high. I moved to Novolog Mix 70/30. Their A1Cs came down, and they gained 20 pounds. I added Symlin, they lost the 20 pounds.

KC: Wow. So you're really talking about the standard of care changing?

DK: You bet. Because it's not okay for a patient with type 2 diabetes to have an A1C above 7. It's not okay for them to have substandard care. It's not okay for them not to have education. It's not okay for them not to understand medical/nutritional therapy and physical activity. It's not okay. It's not okay for them not to be measuring blood glucose. And the key is, everyone needs to take type 2 diabetes seriously and so do their providers.

KC: Building on this notion of what is good for patients … do you see Byetta being used as monotherapy?

DK: Yes, yes, yes, yes, yes.

KC: This will happen?

DK: Absolutely. Why wouldn't you use it as monotherapy?

KC: Okay. My current favorite question of you experts. Are there clinical trials that you really want to see happen that are not being done? Say you could choose two trials and make them happen, what would you do?

DK: What would I do? You know what? I don't think it would deal with drugs, Kelly. I think we all know that education makes a difference. And I do think that there are studies that support education makes a difference. I think we need to do more studies that prove that and use them for better reimbursement for education so that patients get the education they need to be successful. That's where I would focus.

DK: And some studies are underway right now, but it's not enough. I think that industry will benefit the most from supporting reimbursement for educators. I think they should use some of their lobbying efforts to help get that reimbursement. I think studies to support that would be helpful. Not just drug studies, not just device studies, but studies that would support education.

KC: Davida, thank you so much. Talking to you is always so inspiring.

3. Conference Report: American Diabetes Association (ADA) Research Symposium: Advanced Glycation End Products and Diabetic Complications: Insights into New Mechanisms and New Therapeutic Targets. March 17-19, Cambridge, MA

In recent years, ADA has put together research symposia – meetings of great interest to us given their intense focus on a relatively narrow aspect of diabetes. Given our interest in diabetic complications, we were excited to attend the ADA research symposium for Advanced Glycation End (AGE) products in Cambridge, MA, from March 17-19, 2006. The conference brought together 150 participants from academia and industry, with geographical representation from the U.S. as well as Europe and Canada.

As indicated by the title, the three days of oral presentations and the related poster session were devoted to the current understanding of the biology of advanced glycation end products (AGEs), which are reactive chemicals derived from glucose that interact with components of the cell and/or serum in a non-enzymatic fashion to produce cellular damage. It is the damage caused by these AGEs that are thought to cause the long-term micro- and macrovascular complications of diabetes, most notably diabetic retinopathy, neuropathy, and nephropathy, as well as cardiovascular disease. As such, there is much interest in developing related compounds, though to date, this area has not been fruitful commercially.

Despite the seemingly narrow scope of topic, the lectures were quite diverse, ranging from bioorganic chemistry talks, replete with chemical structures and reactions, to cell biology talks on cardiovascular disease and Alzheimer's disease and the all-important results of clinical trials that are of course of great interest to industry.

We include below what we saw as the highlights of the conference as well as detailed notes from the introductory session of the conference. Due to space constraints, we are limiting our conference coverage, but if you'd like read our ten-page comprehensive conference report, please contact reports@closeconcerns.com.

Take away messages:

- We are still defining the biologically relevant AGEs in diabetes, but we can use the strong correlations of AGEs concentrations in the blood and skin as a predictor of diabetic complications. Given the very high percentage of costs of diabetes related to complications, this was particularly interesting due to potential clinical applications, though this research is "early stage."

- The molecular mechanisms of how AGEs cause the complication of diabetes are beginning to be understood. Receptors that bind AGEs and mediate their effects have been cloned and studied in cell culture and mouse models. AGEs provoke an inflammatory response that may be the underlying cause of the kidney, eye, peripheral nerve and cardiovascular damage that occurs in diabetes.

- The role of AGEs in cardiovascular disease was one of the most interesting aspects of the conference. Indeed, one of the most provocative remarks of the conference was made by Dr. Peter Libby, who proclaimed that "diabetes is a vascular disease that sometime manifests itself as hyperglycemia." Toward this end, data were presented that showed how AGEs increase inflammation, which in turn, promotes atherosclerosis and vascular disease. Dr. Beisswenger presented data that demonstrated that tight control of post-prandial glucose levels reduce AGE levels in the serum; other studies were also cited that demonstrated that control of post-prandial glycemic excursions can reduce the onset of cardiovascular disease (Ciriello, *Diabetes* (54):1). We believe this is important because it provides yet another reason why post-prandial glucose levels should be reduced.

- Two trials showing drugs designed to break down AGEs were both negative. This was disappointing in terms of direct drug development implications; however, knowledge on AGEs in terms of power of AGE reduction has not been firmly established. At the same time, it appears that reducing post-prandial hyperglycemia in order to reduce oxidative stress stemming from AGEs is a positive idea.

- Dietary AGEs may be a previously underappreciated source of AGEs for both diabetics and non-diabetics. Animal studies with reduced AGE-diets were quite convincing of their role in treating and preventing diabetes; while human studies have not been as impressive, there is limited data – not enough to form a conclusion, at this stage, in our view.

- There have not been many clinical trials testing whether the inhibition of AGEs can have any benefit. The trials conducted so far have been either small or under-powered, or large without significant positive results. The inhibition of AGE products may serve a role in prevention, but do not do much for treating existing pathology.

- The specific pathophysiology of how AGEs cause diabetic complications is still not completely understood. In some cases, the pathology is known at the molecular level. For instance, work from Dr. Michael Brownlee's lab of the Albert Einstein College of Medicine has pinpointed a specific AGE that accumulates in cells as a result of hyperglycemia called methylglyoxal. They have shown

through elegant molecular biological studies that methylglyoxal binds to certain transcription factors (proteins that promote the expression of other genes), which causes higher levels of proteins that are involved in diabetic complications (like angiopoietin). Thus, some intracellular (endogenous) AGEs have been chemically identified and shown to cause specific molecular defects linked with diabetes.

- On the other hand, the role of the involvement of dietary (exogenous) AGEs in the pathogenesis of diabetes is not completely understood or widely accepted. Some of the problems are technical. The specific chemical species of dietary AGE that cause the problems in various rodent models of diabetes have never been isolated. Most of the studies done were carried out by an antibody that was generated against carboxymethyllysine (CML). It is unknown whether CML is a marker or mediator of pathology; however, since the antibody can be use to identify levels of CML (and hence AGEs) in tissues and serum, it is widely used as a proxy for AGE levels. Thus, it is difficult to conclude that all dietary AGEs are bad; it is vital that the active species be identified through mass spectrometry or some other means.

- AGEs have been *correlated* with diabetic complications and worsening outcomes, but then again, increasing AGEs are due to hyperglycemia, which has long been known to cause diabetic complications.

- Receptors have been identified that bind to AGEs, but the specific AGEs that activate these receptors (specifically the different pro- or anti-inflammatory receptors) are still not known. Thus, the field of AGE biology is growing rapidly and could produce some exciting results that might change the way diabetes is treated given the strong results from work in laboratory animal models. The next step is to determine whether this pathology holds true in human diabetics as well. Moreover, some fundamental experiments are required, especially in the field of exogenous AGEs, before AGE biology can grow to broader acceptance. Currently, AGEs may serve a useful role in predicting diabetic complications, but so far targeting AGE production or formation has not proven to be a viable strategy in treating or preventing diabetic complications. Thus, the jury is still out, but the future is certainly exciting should some other basic work be done.

Selected AGE Session Notes:

Session #1: Chemistry and Biological Properties of Advanced Glycation End Products (AGE).

In high concentrations, glucose can react with proteins in the blood and within cells to form what are known as advanced glycation end products (AGEs). The reaction that produces these AGEs is called the Maillard reaction, which involves the reaction of the reduced form of a sugar (the linear, or aldehyde form of sugar) with the amino (nitrogen-containing) portion of an amino acid or protein. This process occurs without an enzyme, which are protein catalysts that carry out nearly all the reactions in your body. Although this reaction sounds rather abstract, it is the same process that causes the browning of toast or meat when it is cooked. Simply put, the same process that produces toast at the macroscopic level produces AGEs at the microscopic level in the body of diabetics.

The AGEs that form in diabetes cause many effects, including the crosslinking of proteins in a structure called the basement membrane in the kidneys and nerves. This thickening of tissue is thought to be a mechanism for the development of nephropathy and neuropathy in diabetes. AGEs are thought to have a significant effect in the kidneys because they are excreted by the kidneys, but unfortunately also target them as well. Not surprisingly, the level of AGEs in the serum is highly correlated with eventual kidney failure in people with diabetes.

The first two presentations of the session by Paul Thornalley, Ph.D., from the University of Essex, UK and Vincent Monnier, M.D., from Case Western Reserve University reviewed the basics of AGEs and highlighted current technologies that detect AGE levels in patients to try to determine their risk of developing complications.

The major AGE that is produced within cells is methylglyoxal (MG), which is formed through the cellular process that metabolizes glucose, called glycolysis. The reactions of glyoxal (a form of methylglyoxal) with lysine forms an AGEs called carboxymethyllysine (CML). An antibody-based detection system has allowed CML to be the most widely studied AGE.

Although it is possible to use antibody-based assays or more powerful mass spectrometry-based methods to detect AGEs, these techniques are generally prohibitive due to cost or invasiveness (requiring blood collection). Another technique to identify AGEs in patients is to measure autofluorescence in the skin collagen. Dr. Monnier argued that local markers are a better indication of AGE levels than serum AGEs since in tissues there are not many mechanisms to inactivate AGEs (like in the kidney or retina), whereas in the serum, AGEs can be inactivated by binding to proteins in the blood (your blood normally contains proteins like albumin to regulate water balance).

Timothy Lyons, M.D., of Oklahoma University Health Science Center presented data from a clinical study of 96 diabetics and 78 controls that demonstrated that AGE products in the skin are closely linked to the development of retinopathy. The average A1c of the diabetic patients at the time of the trial was 8-9%. He showed some striking pictures of human collagen fibers (protein that makes up our skin) from the study that showed that a 30-year-old uncontrolled diabetic collagen looks similar to that of a normal 70-year-old person. He highlighted the use of skin autofluorescence as a non-invasive way to study AGE formation. (See also *Diabetes* 2005 Nov; 54(11): 3103-11.)

Our next question was, of course, how autofluorescence would work. A poster from Veralight Corporation (Albuquerque, NM) showed that skin autofluorescence could be used to detect impaired glucose tolerance (IGT) in a non-invasive manner. Skin autofluorescence was directly compared to fasting plasma glucose levels and found that while fasting blood glucose of 100mg/dL had a 51.8% sensitivity and 79.0% specificity, the skin autofluorescence technique had a sensitivity of 65.2% and 79% specificity. The trial enrolled 324 individuals ranging in age from 21 to 88. As at DT&T in San Francisco in November, a more basic poster on work by the company also raised the question of the extent to which this technology could diagnose complications as well as IGT.

Jay Heinecke, M.D., from University of Washington, proposed that some AGEs result from the direct attachment of an oxygen or chlorine atom to proteins - this is known as oxidation. In general oxidation is bad—it is thought to be the culprit that causes wrinkling skin, atherosclerosis and now, diabetes. Cells of the immune system, like macrophages and neutrophils, contain oxidative enzymes (such as myeloperoxidase) that are normally used to kill foreign microbes. In diabetes, these immune cells are activated and will actively oxidize lipoprotein particles—both LDL and HDL.

AGEs and cardiovascular disease

Paul Beisswenger, M.D. of Dartmouth Medical School and Peter Libby, M.D., a world-renowned cardiologist, of Harvard Medical School presented talks about the role of AGEs in cardiovascular disease. As they were quick to point out, patients are often terrified of the morbidity of diabetes (such as loss of vision), but such complications ultimately affect fewer of them than does cardiovascular disease, which is responsible for the deaths of far more patients. Kidney failure, too, is far more common than might be suggested by levels of patient fear. Dr. Libby proclaimed at the conference that "diabetes is a vascular disease that sometime manifests itself as hyperglycemia" – for us, this was basically a slightly more

provocative way to say that having diabetes is the same as having a cardiovascular risk factor. Toward this end, data were presented that showed how AGEs increase inflammation, which in turn, promotes atherosclerosis and vascular disease. Dr. Libby reviewed the mechanisms of this effect: the oxidation of LDLs and HDLs promotes their uptake by macrophages to create so-called "foam cells," which then secrete cytokines to attract neutrophiles and other cells (like smooth muscle cells) to create the vascular plaques.

Dr. Beisswenger presented data that demonstrated that tight control of post-prandial glucose levels reduce AGE levels in the serum and advocated the use of Lispro to achieve tighter glycemic control (Ahmed, et al *Diabetes Care* 2005 Oct;28(10):2465-71). Other studies were also cited that demonstrated that control of post-prandial glycemic excursions can reduce the onset of cardiovascular disease (Ciriello, *Diabetes* (54):1), and Dr. Beisswenger also stated that he observed reduced cardiovascular events in his studies.

—by Cullen M. Taniguchi

4. Diabetes UK – Top Ten Takeaways

We jetted over to Birmingham, England for Diabetes UK March 29-31. As always, we were intrigued by the differences between European and American care, thinking, and product focus. We highlight below our top ten learnings from the meeting, which featured everything from public health to basic science.

1. **The UK has not escaped the crushing tide of obesity.** At the Takeda-sponsored symposium titled "Clusters of Cardiovascular Risk – A Pandora's Box," Sara Da Costa, Diabetes Nurse Consultant, outlined what this will mean for cardiovascular health: one kilogram of weight approximately increases one's risk of diabetes by 4.5%; one kilogram of weight loss adds three to four months onto an individual's life. Check that out! A 10% weight loss is associated with a 30-40% decrease in death related to diabetes (based on a 100kg person). Nine out of ten diagnoses of diabetes occur in individuals who are overweight, and 58% of diabetes globally is associated with obesity. In England in 1980, 5% of the population was obese, and by 2010 25-30% will be obese. (In the U.S., one-third of our population already has achieved this milestone.) As in the US, clinicians and patients are blatantly failing to achieve guidelines of cardiovascular health. In the UK, the National Institute of Clinical Evidence (NICE) has established guidelines for target lipids, cholesterol, blood sugar and blood pressure, but these standards have not translated to population-wide improvements in cardiovascular health.

2. **Both diabetes and gender greatly increase one's risk for both fatal and nonfatal CV events.** Among those without a background of CHD, diagnosis with type 2 diabetes increases risk three times; history of CHD but not diabetes increases risk five times, and history of both CHD and diabetes increases risk by a factor of 12! Gender correlates with different levels of risk, as well. The British Medical Journal published a meta-analysis on cardiovascular health according to gender. After age adjustment, women are at 3 times greater risk of CVD death if they have diabetes while men are at 2 times greater risk. These numbers demonstrate that preventing that first event greatly reduces the incidence of a cardiovascular event as one event seems to lead down a path of morbidity and eventual mortality. Stay strong. As Marion Nestle, whose book *What To Eat* will be published May 2, says "*It's all simple ideas. Eat less. Move more. Eat fruits and vegetables*."

3. **The incidence of diabetes will explode in the next 60 years to 366 million cases—developing primary prevention is key.** Dr. Mike Engelgau from the CDC Atlanta opened a panel on primary prevention of type 2 diabetes with some unsettling statistics demonstrating the crucial need for efforts in this area in the coming years. Across the world in 2000, 171 million people had type 2, and by 2060 this number will have likely increased to a crazy 366 million. In addition, much of the increasing prevalence will emerge in the developing world. Engelgau proposed some anthropological

explanations for these increases; given that humans populated the world without trains, cars, planes, and escalators, in a way we have engineered our own epidemic, a "design mismatch." Preventing type 2 demands our attention, Engelgau said, because diabetes alone is difficult to treat, and only leads only to further complications. (With GLP-1, is that really true?)

4. **In the UK, nurses will soon be licensed to prescribe many medications, in an effect to enhance continuity and streamlining in chronic care.** Beginning on May 1, 2006, nurses will be able to prescribe all licensed medicines on the British formulary. Currently, nurses are licensed for supplementary prescribing, which means that a professional assesses and diagnoses a patient, the nurse and doctor then draw up a clinical management plan together, from which the nurse can continue writing prescriptions for the patient. This approach will likely continue even after May 1, since not all medications will be licensed on the formulary and not all nurses will feel comfortable prescribing without the input of an attending physician. In a survey of 863 participants, barriers to nurse prescribing cited included an inadequate formulary, implementing the clinical management plan (i.e. provider cooperation/ commitment), lack of a prescription pad, lack of confidence, and objection by medical staff among others. In addition to the barriers facing nurses already trained and registered to prescribe, many nurses reported being unable to access training to become a qualified prescriber. However, many of these nurses said they would have participated in such a program if it were accessible. Nurse prescribers benefit everyone as it saves patients and professional's time, improves nurses' sense of satisfaction, enhances nursing autonomy and confidence, improves completeness of care from a patient's perspective, and improves relationships, teamwork, and respect among various providers.

5. **In the Dorothy Hodgin Lecture, Dr. Brian Walker presented on 11HSD1, a red hot and getting hotter enzyme that is theorized to drive the excess production of cortisol, leading to metabolic syndrome.** Different factors including glucocorticoids, stress, insulin, and estrogen influence expression of this enzyme. Upregulation occurs in adipose tissues while down-regulation occurs in the liver, without influencing whole body kinetics. Fat distribution correlates to cortisol levels. Studies show that in comparison to lean subjects, obese subjects generate a substantial amount more of cortisol in the adipose tissue. Eating habits may effect cortisol production as well. Levels of cortisol increase in individuals who follow a high fat diet or have greater fat deposits in the body. Other studies have shown that subcutaneous adipose cortisol production distributes cortisol to other parts of the body, while visceral adipose tissue produces and delivers cortisol to the liver. The subsequent pathway that leads to MS is unknown, but such direct effects on the liver likely hint at the connection between obesity, visceral fat, IGT and MS. Further research on the role of 11HSD1 could offer new approaches to reducing risk of CVD. Higher levels of glucocorticoids seems to lead to higher incidence of CV events through their effect on blood vessel walls. However, 11HSD1 knockout mice exhibit no change in vascular function. Companies including Johnson & Johnson, Merck, Wyeth and others are funding research on the inhibition of 11HSD1.

6. **Speaking of glycemic variability, in the UK, the discussion is still about fasting glucose.** This is in contrast to what we've seen here in the U.S., as is obvious throughout this entire issue – the buzzwords now are glycemic instability – and post-prandial as a phrase is suddenly garnering more respect. But at the Sanofi-sponsored symposium at Diabetes UK, Dr. Mike Baxter emphasized the importance of fasting blood glucose for treating patients with or developing type 2 diabetes. He said that though both fasting and post-prandial hyperglycemia are significant to assess cardiovascular risk, they influence different aspects of the disease course. Baxter explained that fasting glucose is particularly important when a patient's A1C is less well controlled. If focus remains on fasting blood glucose, A1Cs can reach 7%. (Of course, we know from Dr. Louis Monnier's prior work that postprandial glycemic control comprises a larger proportion of the A1C when A1C is lower.) Even slight improvements in A1Cs generate a large risk reduction for micro- and macrovascular

complications, with the tightest correlation with microvascular events. (Macrovascular risk reduction requires a greater decrement in A1C. For example, 1% decrement in A1C translates into a 14% reduction in MI rate.) Baxter explained that drug therapies introduced to address fasting blood glucose are different from those designed to address post-prandial blood glucose. For type 2 diabetes, an oral hypoglycemic such as metformin or glitazone in the first stage, followed by the addition of baseline insulin in the second stage target a fasting blood glucose of 5.5-6. Targeting postprandial glucose requires the addition of bolus insulin in a subsequent stage. (We note that Baxter identified meal-time insulin as the fast-track to low postprandials, whereas in the U.S. there has been excitement about incretin therapy and its influence on postprandial blood glucose.) Dr. David Owens spoke next from the opposite position, arguing for the significance of post-prandial hyperglycemia for patients with type 2. Excellent! Few understood the importance of glycemic levels for cardiovascular risk until Kussisto et al published data in the 90s. Since then, many trials have demonstrated that postprandial glycemia is a risk factor for CVD, and specifically glycemic levels 1 hour postmeal (Honolulu Heart Program). In 1999, the DECODE study showed that increases in postprandial, but not in fasting glucose, dramatically increase risk of death from CVD. Just a reduction of 2mM reduced the rate of premature deaths due to asymptomatic CVD by 28%.

7. **Dr. Ronald Kahn of the Joslin Diabetes Center presented the Banting Lecture on the Diabetes Genome Anatomy Project, which has focused on understanding the relationship between insulin and gene expression.** (Just several weeks later, we saw him give a jaw-droppingly good talk at AACE in Chicago as well – he is everywhere!) Beta-cell deficiency, insulin, and diabetes influence levels of gene expression. Beta-cell deficient mice treated with insulin have been used in research on gene expression. A comparison of levels of gene expression (via mRNA) found that in completely uncontrolled type 1 diabetes, 513 genes of 10,000 they tested changed: they either were upregulated or downregulated. Often, this change was not dramatic, but even these small changes are significant, as they are reproducible and occur in a coordinated manner, controlling metabolism in lipids and mitochondria in skeletal and to a greater degree in cardiac muscle. Some of these changes in gene expression were due to an insulin deficiency, and some were due to diabetes more directly. To separate which expression changes were due to each, researchers compared gene expression in a diabetic mouse that is not diabetic but cannot use insulin properly. Of the 513 genes that changed in the diabetic animals, only 130 changed in this mouse model, implying that only this fraction of genes are directly insulin-regulated.

8. **Dr. Kahn believes that ARNT is a key factor in the changes in gene expression.** ARNT is an aryl hydrocarbon receptor—a transcription factor—involved in nuclear transport. It is associated with chloracne, liver toxicity, cancer, and type 2 diabetes. ARNT may be a master switch; mouse insulinoma cells with reduced levels of ARNT exhibit limited ability to respond to glucose. Furthermore, decreasing levels of ARNT lead to lower levels of HRF, IRS2 and Akt2 thereby reproducing some of the changes in the glycolidic pathway. The most definite evidence of the significance of ARNT has been the manipulation of mice deficient in ARNT but only in pancreatic cells. These mice when stimulated with glucose fail to exhibit first phase insulin secretion response, i.e. IGT! Furthermore, the level of gene expression in these mice correlates to levels of gene expression in humans with type 2. This is a lot to ponder for one day.

9. **Dr. Tony Barnett helped clarify the evidence for drug therapy and CV health.** He first addressed treatment with statins, quoting the Scandinavian Simvastatin Survival Study showed a 22% reduction of coronary events with 40mg statin. The *Lancet* published a study called CARDS in 2004 on optimizing statin treatment that showed a 37% drop in related risk with atorvastatin. Another study, MICROHOPE, demonstrated a 25% risk reduction of MI, stroke, and CV death associated with the use of ramipril. Though the causal mechanism is still unclear (directly reduced by ramipril? As a result of lowered blood pressure?) the correlation is obvious. Finally, Barnett quoted the LIFE study

favoring statin treatment (Losartan) over a beta blocker (Atenolol). Likewise, there is a strong evidence base for certain drugs designed to treat other conditions. In the treatment of renal disease among type 2 patients, one study favored a bigger dose of irbesartan over either a smaller dose or amlodipore; UKPDS research recommends metformin to treat glycemia; CARDS and HPS (Heart Protection Study) recommend statins to lower lipid levels; and MICROHOPE recommends a combination of ACE-1/ARB/and Ca blocker, to treat hypertension. If these first line drugs do not work, the research supports pioglitazone, fenofibrate, and diuretics to treat glycemia, dyslipidemia, and hypertension, respectively.

10. **Large-scale research studies offer insight on primary prevention.** Engelgau presented numerous studies that demonstrate the scientific evidence base for prevention efforts. TRIPOD, a study in the U.S., demonstrated the effectiveness of pioglitazone for pregnant women to prevent the onset of type 2. This is the key TZD prevention study to date. XENDOS, conducted by European and American researchers, treated obese individuals with Xenical effectively preventing diabetes. The Indian Diabetes Prevention Program also delayed onset by administering metformin. In China, the Da Qing IGT and Diabetes Study observed a 30% reduction in progression to diabetes through diet changes alone. The Diabetes Prevention Study in Finland implemented an intensive lifestyle change program and observed a 58% reduction in progression to diabetes among individuals with IGT. Significantly, in this study, reduction in risk of diabetes reflected the number of intervention targets achieved by the end of one year following the initiation of the program. In other words, it only matters that you achieve a set of health goals, not how you achieve them.

--by Alyssa Shell and Erin Kane and Kelly Close

5. Attempts to reproduce Dr. Denise Faustman's cure of type 1 diabetes in mice published in *Science*

In 2001 and again in 2003, Dr. Denise Faustman of the Massachusetts General Hospital reported that she had cured diabetes in mice. In mice, a technique of disabling the immune system and transplanting spleen cells resulted in the reappearance of brand-new beta cells, implying that the cells regenerated. The results were hotly contested. They went against conventional wisdom that organs, with the exception of the liver, cannot regenerate. Dr. Faustman's question framed two questions for other research teams: 1) Could beta cells regenerate if immune destruction were halted? 2) Could the spleen cells have been the source of new beta cells? Now in 2006, three reports have been published by independent teams. They corroborate her work on the first point (though to a lesser degree) but not the second.

In their original work, Dr. Faustman and her team first disabled the immune system, then injected donor mouse spleen cells into the diabetic mice—a protein complex on these cells plays a key role in teaching new immune cells to recognize the body's own tissues. While they had planned to follow this with the introduction of donor islet cells, they found that the mice were producing normal islet cells and secreting insulin. Dr. Faustman conducted further experiments to understand whether these islet cells were regenerated from the mice's own islet cells or whether the spleen cells had differentiated into islet cells. If it were the first, that would indicate that type 1 diabetes—and possibly other autoimmune diseases, such as lupus or rheumatoid arthritis—could be cured by halting the immune destruction and allowing the needed cells to regenerate. Most adult organs are not thought to have regenerative capabilities. Further experiments by Dr. Faustman's team suggested that the new islet cells came from both the donor spleen cells and the mouse's own body. In 2003, Dr. Faustman said, "We've found that islet regeneration was occurring and that cells were growing from both the recipient's own cells and from the donor cells."

Three teams of scientists published in *Science* (March 24) the results of their attempts to reproduce Dr. Faustman's results. Researchers at the University of Chicago, Washington University in St. Louis, and the Joslin Diabetes Center reported that they successfully cured mice with type 1 diabetes, but none of the groups could confirm Dr. Faustman's finding that the islet cells came from donor spleen cells. Two groups said that the islet cells came from the diabetic mice themselves, and one group said the question could not be answered. Much of the initial attention around Dr. Faustman's findings had focused on the possibility of spleen donor cells, as people hoped that relatives of those with type 1 could donate spleen cells to cure diabetes. Recent work from Dr. Doug Melton's group (molecular and cellular biology expert - www.mcb.harvard.edu/melton/) has shown that the primary source of beta cells in mice is the pancreas, and not a stem cell precursor (Dor, et al, *Nature* 429(6987):41-6). The findings from these three studies are in agreement with Melton's work, where it appears CFA (Complete Freund's Adjuvant) treatment suppresses autoimmunity to the point where the normal regeneration of beta cells can occur to replenish the population.

We highlight Dr. Buse's comments on being cautious about extrapolating the recent *Science* findings to humans. Though mice are useful models, experiments in mice often have very different results in humans, and the mouse immune system is very different from the human immune system. As Dr. John Buse told the *New York Times*, "If I was a betting person, my guess is that it probably won't work in humans." Regardless of whether it would work, the technique that the researchers used to halt the autoimmune destruction in mice is too toxic for use in humans. If, however, beta cells can regenerate or survive autoimmune destruction, researchers could seek other ways to stop autoimmunity and could then cure diabetes without requiring a source of islets. Many research efforts today, such as stem cell research, islet cell transplantation, etc., assume that people with diabetes need a replacement islet cell. If the replacement cell could come from their own bodies, this would remove one of the major hurdles in work toward a cure.

Thus, the findings of the reproducibility experiments are mixed. There are many basic science experiments that go well that do not receive this kind of publicity, and we note that the experiment is still early stage. In her piece in the *New York Times,* Gina Kolata took an optimistic tone, highlighting the finding that islet cells were regenerated when the immune destruction was disabled. In contrast, Jennifer Couzin's piece in *Science* magazine characterized the experiments as a failure, emphasizing that the finding that spleen cells were responsible for the successful islets was not replicated. The difference in the headlines—"A Controversial Therapy for Diabetes is Verified" versus "Diabetes Studies Conflict on the Power of Spleen Cells"—shows the stark difference in interpretation of the two writers.

The *Wall Street Journal* article focused on the clinical trials that Dr. David Nathan will lead at Harvard as a follow-up to these findings. These human trials will inject diabetic volunteers with BCG, a compound that destroys T cells as was done in Dr. Faustman's murine experiments. Researchers hope that targeting T cells may allow regeneration of beta cells in the volunteers, restoring insulin secretion and glycemic control.

Still, the controversy continues. After the new studies were reported in the press, many researchers were critical of the way Dr. Faustman presented the new findings. The Joslin Diabetes Center issued a cautious statement on its website to patients (available at http://www.joslin.org/1083_3312.asp), using the word "cured" in quotation marks and noting the wide variations in rates of reemergence of islet cells (16 to 35 percent in the recent studies versus 90 percent in the 2003 Faustman study). In a press release, investigators from Joslin discounted the upcoming work with BCG, stating that previous trials "large enough to be informative" failed to show any positive effect.

In our view, the results of these experiments are positive, as it is very rare that early scientific work gets systematically reproduced, but we are far from having a cure for diabetes. It is important not to

lose sight of the fact that the mice regenerated islet cells in these experiments, something that was previously believed to be impossible. The treatment of CFA in the foot pads of mice is very different from the BCG inoculation that Dr. Faustman proposes. At this point, however, there is some scientific consensus that CFA treatment works to reverse diabetes in mice, though the degree of success varies and the source of new beta cells is not yet clear and differs from Dr. Faustman's original study.

Dr. Nathan and Dr. Faustman were featured on NPR's Talk of the Nation, where Dr. Nathan supported Dr. Faustman enthusiastically, emphasizing that Dr. Faustman's main finding—the reappearance of islet cells—was replicated three times by separate groups. They postulated that the level of glycemic control in the mice may have affected whether or not the islets regenerated, as tight glycemic control is believed to be essential for islet survival, and mice who did not have tight blood sugar control may have lost islets for that reason. This was given as an explanation for the differing rates of success among the groups. Dr. Nathan spoke to the next steps, saying, "Our first step in human studies will be to look at whether we can suppress these T-cells in humans . . . Curing anyone is a long ways away."

—by Erin M. Kane, Cullen M. Taniguchi, and Kelly L. Close

6. Outstanding BIO panel in Chicago cuts through the clutter

In mid-April, the 14th annual BIO (Biotechnology Industry Organization) was a fascinating mix of science, business, vision, politics and entertainment. Headline grabbers included former US President Bill Clinton and the current U.S. Health and Human Services Secretary Michael O. Leavitt, not to mention ethanol-fueled race car and Indy racecar driver, an indoor cornfield, and Magic Johnson. No wonder the heads of the major pharmaceutical companies and governors from 12 U.S. states joined over 19,000 attendees from 62 countries.

Among the wide-ranging topics covered in the conference, we were as always hyper-focused on items related to diabetes – this time, on metabolic syndrome, with a panel titled "Early-Stage Business Models in Metabolic Disorders." Panelists, led by moderator Nicola Campbell of Sofinnova, included VC Kathy Tune of Thomas, McNerney and Partners; Dr. Bernice Welles, Vice President of Development at DiObex; Robert Mashal, President and CEO of Alinea Pharmaceuticals; and Prof. Frank Greenway, Chief of the Outpatient Clinic at the Pennington Biomedical Research Center. The panelists shared their thoughts on metabolic syndrome, focusing on the potential for drug development for this indication.

First, it's big. Although metabolic syndrome isn't universally recognized and controversy continues about its definition, panelist Dr. Bernice Welles, DiObex VP of Development said, "About 25% of American adults have the metabolic syndrome (based on NCEP/ATPIII criteria), and this could translate into as many as over sixty million Americans."

Despite the size of the prospective market, metabolic syndrome is not an easy target for drug development, in part due to controversy over the definition and the incredulity of the FDA. As Dr. Welles noted, "Recently, the ADA/EASD have taken a stance that downplays the utility of focusing on the metabolic syndrome, while the AHA has come out focused on the syndrome. (See Kahn R., Buse J., Ferrannini E., et al.: The metabolic syndrome: Time for a critical appraisal: Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 28: 2289-2304, 2005; See Grundy, Cleeman, Daniels, et al: Diagnosis and Management of the Metabolic Syndrome: Joint statement by the American Heart Association and the National Heart, Lung, and Blood Institute. *Circulation* 2005; 112: 2735-2752.) "One area of agreement is that the use of the term MS is useful for clinicians as it serves as a way to identify patients at high risk of developing both type 2 diabetes as well as cardiovascular disease."

As panelist venture capitalist Kathy Tune of Thomas McNerney said, metabolic syndrome does fit some of the standard investing criteria. While this appears to be a very large market with significant unmet needs that doesn't mean, said Tune, that it's going to be an easy target for drug companies since "[n]either the regulatory path for approval of a metabolic syndrome claim nor the reimbursement path is clear." That's perhaps an understatement. Tune said that it was clear to her from the panel that "the FDA is not even close to outlining what it would take for a drug to receive a metabolic syndrome label claim. Without a consensus definition of the syndrome, it would be difficult if not impossible for the FDA to issue guidelines for approval of a drug for the syndrome. It would appear we are many years away from such a set of guidelines."

Dr. Welles concurred, emphasizing that the challenging of addressing metabolic syndrome is that its claims to legitimacy are tenuous. She said, "We do not yet know what causes it, or whether it really is a syndrome. Physicians can prescribe lipid lowering drugs, anti-hypertensive drugs, insulin sensitizing agents, and tell people to diet and exercise. Each of these actions has some success, but we really do not know how to treat the syndrome."

The costs of developing a drug for metabolic syndrome will be high. At the panel, concerns over the safety of a drug for metabolic syndrome were discussed length, not surprising given the number of safety concerns over drugs that have arisen in the past few years. According to Tune, "the implications for small companies and in particular for companies developing new classes of drugs and/or drugs to be used in very large populations of patients are far reaching. These small companies may very well need to spend significantly more money and take longer to gain approval for these new clinical entities and new indications than they have in the past." What's more, even choosing patients for a trial may be challenging, due to the controversy around the definition of metabolic syndrome, Mashal pointed out.

To boot, despite the fact that a drug for metabolic syndrome would be one that improves multiple health parameters, the FDA application process currently will assess a drug for a single indication only. Mashal said that the FDA will likely continue to evaluate a drug for its effect on one particular component of metabolic syndrome, such as obesity, hypertension, impaired glucose tolerance, abnormal lipid profile, etc., and not consider multiple indications for a drug in one application. Trials that show that improving patients' levels in several of the above areas improve mortality and morbidity for those patients would help, and Mashal said that "from a commercial perspective, clinicians and patients are very likely to differentiate between such interventions, and a compound that affects multiple parameters is likely to have a key marketing advantage over compounds that only affect a single parameter." What this says to us is that while it'll be a long time (if ever?) we see a metabolic syndrome label, there's big focus on the area, and incremental steps may be made – how about a treatment for impaired glucose tolerance, for example? Stay tuned.

— by Leah Edwards and Kelly Close

7. DCU Company Watch

- **Novo Nordisk—Earnings released, Levemir launched, ADA oral presentation for Liraglutide:** Novo Nordisk announced its earnings April 28 – the company continues to benefit from the insulin analog strength, which represented a pretty stellar by any measure 60% of overall company growth of 636 Danish Kroners or about $107 million. Novo launched Levemir (detemir) in the United States March 28, offering the first competition for Sanofi-Aventis's long-acting Lantus.. It was approved by the FDA in June of last year. We heard news of the Canadian launch last fall at the Canadian Diabetes Association meeting, and from there we reported that the Novo marketing team is looking to differentiate its product by highlighting both its effect on weight gain and its variability. Novo has

begun phase 3 trials for 3800 patients for liraglutide, which will take two years plus time at the start and the end – we gather the trials won't actually start til around summer. On a positive note, they announced they will do an oral presentation on its phase 2 b trials. It's tough going, because we can't imagine this would beat Amylin's LAR to market, but then, hope springs eternal….The company announced it has a new oral diabetes drug in phase 1. When asked about Sanofi's Apidra, the company pointed out that Apidra has less than 1% market share (but cut them a break, they have only been out a few weeks! Still we agree it's very hard to differentiate). On the downside, the two mixes received non-approval letters (30/70 and 50/50) – that's certainly a positive for Lilly.

- **Sanofi's – Rimonabant, er Acomplia, er Rimonabant gets EU approval:** Rimonabant has been recommended for EU approval, despite all the psychiatric questions. We recommend reading the press release, because it's like a lovely, lovely letter to the FDA, urging concern over off-label use, discussing cardiometabolic this and that …etc. The name is still schizophrenic – Acomplia was used for the first time again in this release since before the US approvable letter.

- **Conjuchem trials reported – more hype? More hype:** Conjuchem reported on phase1 / 2 trials – the call reminded us of the one a couple of years ago (on this same compound, come to think of it) where the company wanted to stop trading because the results were so meaningful. Conjuchem's late April conference talk covered a lot of ground about trial "*clearly exceeding expectations*," etc. We like it when companies are just straight with investors and lean more toward letting the investors characterize the results than trying to do it for them, so since this is how the call started, we were a bit put off, and this didn't diminish as the call continued. There are a lot of pieces of the study we don't have full information on and while this is always true for every company, at least addressing a bit of it would be nice. The A1cs, for example, were 6.5 to 11 for 42 people. So how many were actually 7 or less? More importantly, how many were 8 or even 9 and above? Why did study participants go off their drug regimen a week before starting the trial? That week must've been rough (especially for anyone with an A1C over 7), and then for them to start a new drug – how surprising is it that people on placebo (i.e., on no drug) would do far less well than people on a new drug, who are suddenly testing 6 times a day?! Why you wouldn't have participants continue therapy is beyond us, so you could show add-on effect. Conjuchem may or may not have a product that can be successful here. This is why investors typically look at Phase 1 and 2 study results pretty cautiously – I was chatting recently with a very savvy investor who mused that 90% of early studies show success 90% of phase 3 trials show failure (see Roche's 483 below, for example – 5000-person Phase 3 trails were ongoing, then the compound is kicked back to Phase 2, then it is dropped – you win some, you lose some). This compound could get to Phase 3 and could show success, and then it will need to address a lot of other complicated issues – dose identification, production scale up, long term safety and efficacy studies, etc. We would imagine it is four years minimum if everything goes right and quickly and there are no hiccups. THEN, in the best case scenario, there may be a competitor to LAR, although the company still may not have a daily product (we imagine patients will always start with a daily incretin and then move to a longer half-life product, assuming the product emerges). Bottom line, the company could clearly meet with some success, but we bet if they do, it will be lucky or accidental. On the partnership front - they have referred to partnership opportunities and proposals they are reviewing for years. Due to the tremendous interest in diabetes and incretins, we wouldn't be blown away if a partner does come out of the mist at some point, particularly if the IP is judged interesting or important – but we wouldn't translate that into a competitive product emerging until after the turn of the decade.

- **Amylin 1Q06 – Strong quarter and potential supply issue:** It is tough to experience supply problems this early on. In the serious cases, capacity issues tend to take longer and hurt more than expected. The classic biotech capacity disaster, of course, is Enbrel – there, the capacity woes significantly shrank the installed base. We don't think this is an Enbrel situation – the supply

constraint has nothing to do with the drug supply, and is "just" the cartridge. That is still problematic and we'll be eager to see this issue behind the company, mostly because we know the docs like samples for the first timers and this could possibly delay a bit more PCP starts – and delay patient benefit, which is what we look at and care about the most. We expect this Baxter cartridge problem to clear up (and obviously supply problems are ultimately a high class problem as long as they are resolved) but we do believe lack of sampling could result in fewer starts – coupons are typically a bigger pain than free sample pens, but then again, the docs all will have the demo pens and there is clearly lots of positive momentum. Big picture, keep in mind – off a $68 million Byetta quarter, and supply issues, if minor, for the company to commit to a $400 million year for Byetta is a very big deal – in fact, it's quite remarkable guidance. We also, as usual, still think Symlin is a sleeper, that it'll have end of the year strength, which translates into better bottom line results since Amylin owns all of it.

- **GSK – Avandia clearly headed for $2.5 billion–plus year:** An excellent Avandia quarter was reported April with total global sales of $602 million for the drug, up 24%. The combo of Avandia and Amaryl has now been launched, and we'll watch this one closely. We think there is good upside for both TZDs and Byetta when the label expansion is approved – TZD patients see so much weight gain and delayed efficacy – Byetta could really help adherence.

- **Bayer 1Q06 – Nice increases for diabetes care:** How excellent that the #3 and #4 glucose monitoring players, Abbott and Bayer, were the ones coming in with growth this quarter! Diabetes Care sales rose 24%, largely due to increased investment in the Ascensia brand, particularly in U.S. - management noted that investment in the fourth quarter of 2005 is showing an impact and led to this accelerated growth in 2006.

- **Roche 1Q06 – R483 PPAR dropped …** Being on top is tough. Growing from such a big base is a killer; first quarter sales for Roche, despite a terrific new product in Accu-check Compact Plus, was slowed by maturation of Accu-Chek Advantage, resulting in a 5% decline in Diabetes Care sales. Management reported that the recent launch of Accu-Chek Aviva, the successor product, has so far only partially made up for declining sales for the Advantage system in the U.S. The launch of Accu-Chek Compact Plus, the integrated test strip system, in the U.S. and Canada should help expand Roche's market leadership position in "this fast growing segment." What gets so much buzz is, believe it or not, something so small, but well loved – the automatic calibration (helps downloading, training, etc – easy, easy easy). Bayer benefits from this as well with its Breeze (see above). On the pharma side, we got an excellent update on products in development for T2 diabetes. In <u>Phase II are:</u>
    - R1440 – enzyme modulator - projected submission post-2009
    - R1438 – enzyme inhibitor -projected submission in 2009
    - R1583 – GLP-1 analogue from Ipsen

  and in Phase I is R1439 and a topical VEGF for diabetic foot ulcers from Genentech. In Phase 0 are compounds R1511 and R1579. What is bigger news is what is *not* happening - R483 was discontinued in Phase II. As readers who have followed this 'novel TZD' rollercoaster will recall, this had been moved into Phase III in 2004, and had been lauded as the best-in-class insulin sensitizer, until it got moved back to Phase II for tox testing with all the other insulin sensitizers. We wrote last month that Roche was waiting for results of its FDA meeting – they weren't positive. As we wrote about this drug in August, 2004, R483 looked from its ADA abstract as though it *might* offer a better way to target PPAR-gamma, as it looked to have higher affinity and binding. But, that was the summer that, in light of the new guidance by the FDA on all PPAR drugs in development, Roche had to wait for further long-term toxicity data to come in before making firm Phase 3 plans. Alas, that wasn't a fruitful two years of rat studies – remember, this was the drug for which 5000-person Phase III trials had already been planned.

- **Abbott earnings—Nice one!** On April 19, Abbott announced outstanding diabetes sales of $273 million, up 11%. In this market – really an excellent showing. Abbott also noted its hope that Freestyle Navigator (continuous monitor) would be on the market by the end of 2006. We hope so too ~ we can't wait for a genuinely thriving commercial market for this technology and we expect an excellent showing from this product. We saw a fantastic AACE symposium by Drs. Irl Hirsch and Howard Wolpert – "Real-Time Continuous Monitoring Implications and Opportunities For the Clinician" and some of the examples using Navigator data really got at the power of this technology and what it could provide patients – and clinicians. In our next issue of DCU, we'll go through the high points of their presentation, on hypoglycemia and hypoglycemic hypoglycemia unawareness, glycemic variability relevant to microvascular and macrovascular complications, and the role and clinical utility of CGM in reducing hypoglycemia and glycemic variability – as anyone knows that went, these were really standout talks that gave everyone interested in this new technology some incredible learning.

- **MannKind—Intriguing results of type 1 study:** MannKind gave a top-drawer investor presentation April 19, complete with an endorsement of use of inhaled by type 1s by type 1 Dr. Irl Hirsch. MannKind released impressively good results of its study of Technosphere insulin in 110 type 1s on basal/bolus therapy. Participants all used Lantus and were randomized to either Novolog or Technosphere for 12 weeks. This was a terrific meeting and it raises the question yet again who the best partner is. Ironically, we probably think, Novo Nordisk. Back to the study:
    - **A1C:** Significant, roughly equal drop in both: 0.83% with Technosphere, 0.99% with Novolog.
    - **Postprandial:** Technosphere dominated here. The mean glucose rise after a standard meal was 18.7 mg/dL in the Technosphere group compared with 46.8 mg/dL in the injectable group. The postprandial total fluctuation as measured by AUC (area under the curve) was 582.8 with injectable insulin and only 232.9 in the Technosphere group. We liked the very detailed analysis and, of course, the focus on GV.
    - **Weight gain:** The Technosphere patient group experienced a 0.41 kg (0.9 lbs) weight loss, whereas the injected rapid-acting insulin analog patient group gained 0.89 kg (2 pounds) ~ a difference of three pounds over 12 weeks.
    - **Pulmonary function:** No difference

  Of note, Technosphere seems to be differentiated from Exubera in terms of speed of effect. While Exubera's pitch is delivery only, MannKind continues to emphasize the speed and more physiological action of Technosphere insulin in addition to its inhaled delivery. There has been some talk of line extensions, and we believe that if MannKind could transform its product into more efficient injectable insulin, there would be significant uptake in other segments of the market. We are not certain of the degree of complexity required but we suspect it is very high.

  We've been skeptical about inhaled insulin for young people and type 1s in particular, as we have concerns about lung safety for insulin administration four to six times per day for 70 years, but particularly in light of the JAMA pieces on glycemic variability (see the literature review in this issue), these study results are certainly strong. Continuous monitoring is also highlighting the need for a faster acting insulin (we're calling it VRAI – very rapid acting insulin) and has shown that while we may call our current insulins "rapid acting analogs," rapid may be a term used only relative to the original regular insulin. We are interested to know how patients' meals were configured. For instance, were they required to eat meals that matched either 3 or 6 units of insulin, as with Exubera, the inhaled insulin currently available (the insulin must be dosed in 3-unit increments, which is large compared to the one unit for injectable and 0.025 unit for pump therapy!) We don't have full dosing precision details for Mannkind.

In his address to investors, Dr. Hirsch emphasized that glycemic variability is pro-inflammatory, and that insulin is anti-inflammatory. An insulin that decreases glycemic variability will help patients reduce inflammation in two ways, he explained. Dr. Hirsch noted that the FDA looks at A1C and fasting glucose—that is *not* what is fueling complications, he said. More focus on post-prandial glucose is coming, and all therapeutic strategies should be evaluated for how they lower GV as well as A1C. He added that he believes MAGE (mean amplitude of glycemic excursion) will be increasingly used as a measure of glycemic control.

If the data continue to support MannKind's efficacy in reducing postprandial peaks, the timing couldn't be better —the convergence of continuous monitoring technology and new data showing that glycemic instability drives oxidative stress and complications will drive demand for a way to control these peaks – there are still safety concerns but the FDA approval is the first step of course toward a viable commercial market. We'll be eager to learn more here at AACE about inhaled insulin and hope to learn more about launch plans – mid summer is the current timing thought. MannKind noted that it is preparing for the commercial phase and driving toward commercial scale and manufacturing. It will be able to supply at least 500,000 patients at launch and 1 mm within a couple of years.

- **JNJ earnings—A flatter start to 2006:** On April 18, JNJ reported 1Q06 earnings. Diabetes was not a big airtime topic – interestingly this quarter, what happened was a 180-degree turn from historical times – J&J and Roche, the big guys with 60%-plus share of this market, had the hardest time, and #3 and #4 players Abbott and Bayer performed swimmingly! So operational growth at LifeScan was 3% in the first quarter, all due to U.S. sales, which grew by 6% while worldwide sales were flat. J&J did comment briefly on Lifescan's acquisition of Animas, saying that its completion "provides Lifescan with a platform for entry into the fast-growing insulin pump segment of the diabetes market." That is for sure. Animas has terrific infrastructure and we believe continuous monitoring will really drive insulin pump growth going forward, so the companies will really be fighting it out to grab those early continuous adopters. At least everyone will be doing it in a growing, if more competitive market. Going forward, it will be difficult to assess blood glucose monitoring growth apples to apples since pumps will be included in the total but not broken out. We would forecast about $100 million for Animas in 2006, but amidst all the change, it's tough to forecast. Okay, so we're saving the best news for Lifescan for last! The Ultra 2 is out and it is slick! Taking a page from some of the most successful therapies ever, Ultra appears to be "easier to use and easier to read" and also has improved messaging, and greater memory capacity. We love it personally and just hope it works with our Dex Com STS.

- **Arkray acquires Medisys's Hypoguard—$43 mm deal, dauntingly low revenue multiple:** On April 18, Medisys announced the sale of Hypoguard, its primary operating unit (main products are glucose monitors), to Arkosys for just shy of $43 million. Medisys (MDY.L) is a small British diagnostics company with 2005 revenue of ~$54 million. The Hypoguard unit develops and manufactures diabetes devices, including blood glucose monitors, lancing devices, and lancets. The majority of its revenue comes from its blood glucose monitoring (BGM) business; its Supreme and Assure monitors give the unit a 28% market share in the long-term care BGM market (a small part of the overall market). The unit has had a rough go of it and we hope Arkray will be the right home. So Arkray is a Japanese diagnostics company, offering products in diabetes, urinalysis, and POCT (point of care testing). This is the company with all the cool monitors at EASD the last couple of years – you remember, if you went, the gold ones? They get the monitoring side and we're still not sure about strip pull through. In June 2005, the company released a new blood glucose monitor called the Glucocard X-Meter, which uses an automatic calibration system, requires only a 0.3uL blood sample, and generates results in five seconds. We saw this meter at EASD in Munich and were very impressed. We know that noise in the market through increased competition and pricing pressure has significantly cut into Hypoguard's profit margin and market share in the BGM business. Hypoguard's

market share in the long-term care segment of the market has decreased from 38% in 2004 to 28% in 2005. The company said that its mail order and retail business have suffered similar declines but did not offer specific numbers. Executive Chairman Dr. David Wong stated, "the Hypoguard Group is well positioned, in terms of product offering and presence, in the blood glucose monitoring market; however, a parent with greater capital resources is required for it to successfully overcome the current challenges it is facing." Medisys now plans to become a medical investment firm focusing on companies in the medical device, diagnostics, biopharmaceutical, and healthcare industries. So whew. This is a new low – a very very new low in terms of multiples paid for a diabetes monitoring company. Figuring out blood glucose monitoring revenue is a little tricky but even say that it is 50% of the business (we suspect it's a little higher than that), that would still only be a 1.6x trailing revenue multiple, very different from trailing revenue multiples of 9-10x in the Medtronic-MiniMed days or even 5+ for J&J's purchase of Animas.

- **Medtronic—FDA approval welcome surprise:** Though not expected until October, Medtronic won FDA approval for its sensor-augmented pump April 12. This is a big upside surprise for the company! The launch will be immediate for the sensor-augmented pump, while the sensors themselves will be available Julyish. We saw an unveiling at AACE and anticipate (if you're in Chicago, by the way, before May 20, go see *Anticipation* at the Museum of Contemporary Art – www.mocp.org/ excellent, whether you love or hate suspense!) an absolute blow out at ADA. The sensors will be priced at parity to DexCom at $35. We hear very strong patient feedback to the product. While MDT can only be thrilled with the FDA right now, it's not as thrilled with CMS – on April 3 that that Medicare health program has rejected Medtronic's request for a new code for its Guardian RT, saying that Medtronic hasn't "proved that its new system for alerting diabetics to dangerous blood-sugar swings is better than older, cheaper tests." In a follow up meeting in late April, progress was made as others came in to support Medtronic in its work toward broader access – it is clear to us that publication must be stressed throughout industry, as much cost-efficacy data. We look for more news here in the fall.

- **Novartis—Galvus accepted for FDA review and the race with Merck begins:** Novartis's March 30 report that DPP-4 inhibitor was accepted for FDA review puts it about six weeks behind Merck's submission and FDA acceptance of Januvia. The press release referred a number of times to alpha and beta cell improvement, suggesting that DPP-4 will both enhance insulin secretion and reduce output of glucose by the liver. The DPP-4 companies appear to be more aggressive in potential claims about beta cell preservation/regeneration – we are not sure why. We expect to see more on this at ADA but we're incredibly far from convinced based on experts with whom we speak who follow this confusing class closely. Indiscriminate enzyme inhibitors – too much confusion for us on what is being activated, what isn't, what it means, and what safety issues could come up, too late.

- **Dex Com received FDA approval March 27. Excellent!** The fast HCP training and small size of product (especially transmitter) represented the biggest wins to us. The company did not submit the 7-day sensor as it said it would, but we imagine this will come shortly – the AACE data was certainly extremely impressive (see aace.com to download). At Dr. Klonoff's Boston clinical diabetes meeting last weekend, one notable doctor said that all doctors and nurses need to be prepared for very emotional responses – two of his patients burst into tears, he said, upon hearing the news.
    - **Training positioned as quick:** Rasdal addressed the HCP training question and suggested that training for the STS will be easier than pump training, as it is not delivering a "potentially lethal" drug like insulin. He said that when they train a center, it requires only a few hours, and that patients can typically be trained in less than an hour – that is FAR, far lower than pump training, and we believe the new reps will be extremely motivated as a result! Because one of the biggest concerns overall is time required by HCPs, they are very focused here. We have heard good things about an easy fax-in tear sheet that HCPs will have for those that want to order.

- **Business model focused on disposables:** Rasdal emphasized throughout the call that continued reorders of sensors are going to drive sales, not sale of a single durable. He said that this was why they wanted to move at an appropriate speed to be able to respond to any problems that might arise in the first week or two because these would be customers "for a long time to come." All replacements will be shipped by Dex Com directly, so it will be key to ensure that their distribution details in place.

- **OrSense—Impressive MARD, though small numbers:** OrSense reported March 22 the results of a 6-patient study of their noninvasive continuous monitoring technology in an acute care setting, finding a stunning 100% in the Clark A+B, a Median Relative Absolute Difference of 11.5%, and a Median Absolute Difference of 18 mg/dL. On the Clarke error grid, the breakdown was 79% A zone, 21% B zone. Prof. Pierre Singer presented the results at the 26th International Symposium on Intensive Care and Emergency Medicine. The study is one arm of three, and we await the results of the group of 30 total patients at three hospitals in Israel. In addition to a focus on the acute care setting, the company is testing its device for use in the outpatient setting, and in 2005 OrSense has been tested in clamp studies inducing hyperglycemia and hypoglycemia as well as in 24-hour simulated home scenarios, the results of which were presented at EASD and DTM.

- **Veralight on a roll at the AGE meeting –** We see Veralight as the biggest corporate beneficiary of the AGE conference in Boston in mid-March and we look forward to hearing much more about their promising trajectory – both on treating patients with diabetes who are at risk of pre-diabetes and diabetes and also those at risk of complications. Excitement abounds …

- **Abbott—Clearing 510k for FreeStyle Freedom:** Abbott Diabetes Care announced March 13 that it had received FDA 510k clearance for its FreeStyle Freedom, a blood glucose monitor that requires 0.3 micro liters of blood and five seconds to read. This is the next generation in the FreeStyle blood glucose monitoring line. Key differentiators appear to be the 5-second read time (slightly better than other members of the FreeStyle family) and better LCD. The Freedom still permits alternate site testing, of course.

- **Amylin—Prices going only one direction ~:** The demand curve has apparently shifted right, because Amylin disclosed March 10 that they are hiking the wholesale prices of Byetta and Symlin. Byetta pens in 5 and 10 micrograms per dose jumped from $147 to $156 and from $173 to $183, respectively. A vial of Symlin will now cost ~$86, up from $80 (all prices rounded up to nearest dollar). Costs per patient vary, but on average, patients pay $2000 - $2500/year. The price ceiling on diabetes drugs has moved up dramatically in the past few years, and initial reimbursement for Byetta and Symlin has been largely favorable because they are seen as (perceived and actual) as novel therapies. Still, Kaiser doesn't yet reimburse and other co-pays remain high; we believe there is more reimbursement upside to come as plans cave to patient demand.

- **Orexigen Therapeutics – New CEO takes the helm:** San Diego-based obesity drug company Orexigen said March 9 that it had named Gary Tollefson as CEO to succeed John Crowley, who left in 2005. In the same announcement, Orexigen announced COO Anthony McKinney, CFO Lynne Rollins, and Chief Scientist Michael Cowley. Orexigen—which has lead anti-obesity compounds Contrave and Excalia in phase 3 and entering phase 3 in May, respectively—has said that its next financing may be an IPO rather than venture capital. The area is certainly hot, and as we know, there are more than enough obesity pathways.

- **Arkal Medical—Funding raised for novel glucose monitoring system:** In December, San Jose-based Arkal closed a $5.3 million Series A funding round for its glucose monitoring technology, the details of which are not yet public. The round included most excellent backing from Delphi Ventures

(~40%), Shellwater and Co. (~5%), and MedVenture (~55%). Alkal CEO Arvind Jina is highly regarded for his success as founding CEO and President of HemoSense, which had its IPO in 2005. MedVenture's Chris Kaster named the size and direction of the market as reasons for MedVenture's decision to invest, and both he and Delphi's James J. Bochnowski have joined Arkal's board. This one bears close watching based on the board alone.

—by Nate Freese, Cindy Glass, Rachael Hartman, Erin Kane, Win Rosbach, and Kelly Close

8. Three questions with Dr. Louis Monnier

Many thanks to Dr. Monnier for taking time to respond to questions from us about what we strongly suspect will be viewed historically as groundbreaking work.

1. Is it possible for you to speculate as to the reason why glycemic variability causes an increase in oxidative stress?

LM: I think that acute and rapid upward or downward glucose variations result in acute changes in cellular (i.e. endothelial) metabolism and in subsequent damages of endothelial cells (see the excellent review of Brownlee. Diabetes 2005; 54:1615-1625).

2. Addressing glycemic variability seems very difficult clinically. Are there other studies you are aware of that are doing this and could you comment on what your ideal study design would be?

To my knowledge the MAGE is one of the best marker of glucose variability. However, this evaluation requires a continuous glucose monitoring over 24-hours. As a consequence I think that continuous glucose monitoring systems should be more frequently used in type 2 diabetic patients, especially for better tailoring of antidiabetic treatments.

3. We have read your seminal work showing the relative contributions of fasting and post-prandial blood glucose to A1C ("Contributions of Fasting and Postprandial Plasma Glucose Increments to the Overall Diurnal Hyperglycemia of Type 2 Diabetic Patients") —could you give us your view on what patients' A1C target and SD and average glucose targets should be?

It is a pleasure to learn that you have read our article in *Diabetes Care* (2003). I would also suggest to you the reading of the letter that we have published in *Diabetologia* (September 2005): The title is: "Should seven be the magic number of type 2 diabetes?" In this letter we suggest that the number seven might be used to indicate a cluster of measures including diagnosis of diabetes (7mmol/L glucose at fasting [ed.note – this is equivalent to 126 mg/dL) interventional threshold for completing treatment (< 7 mmol at 5h after lunch), target for achieving treatment success (< 7 mmol glucose at 2h after lunch) and HbA1c goals < 7%. These suggestions are based on the results of an article that we have published in Eur J Clin Invest 2004;34:37-42.

—by Erin M. Kane and Kelly L. Close

9. Literature Reviews: Articles in JAMA investigate glycemic variability and SMBG in type 2

- **Monnier D. et al. "Activation of Oxidative Stress by Acute Glucose Fluctuations Compared With Sustained Chronic Hyperglycemia in Patients With Type 2 Diabetes." JAMA April 2006. 295 (14): 1681-1687.**
- **Brownlee M. and I. Hirsch. "Glycemic Variability: A Hemoglobin A1c-Independent Risk Factor for Diabetic Complications." JAMA April 2006. 295 (14): 1707-1708.**
- **Saudek, Christopher, et al. "Assessing Glycemia in Diabetes Using Self-monitoring Blood Glucose and Hemoglobin A_{1C}." JAMA. 12 Apr 2006. 295(14):1688-1697.**

In the April 12 edition of *JAMA*, Dr. Louis Monnier and colleagues report an association between glucose excursions and oxidative stress that is independent of A1C. Discussion of glucose excursions, or "glycemic variability" has become more common in the last couple of years, although the relevance of glycemic variability to diabetic complications has been a point of controversy in the past few years, with proponents (like Monnier, Brownlee, and Hirsch) arguing that glycemic variability increases the risk of complications independently of A1C and opponents (like Saudek) apparent arguing that post-prandial scores don't matter (we are closer to the "not enough evidence – let's get more" side). We review Monnier's study and Saudek's commentary in this memo.

Monnier's study included 21 participants with type 2 diabetes and 21 case-controls without diabetes. Blood glucose levels were followed using a continuous glucose monitor (Minimed CGMS). Oxidative stress – which is a metabolic disorder that has been linked closely to vascular disease - was measured using 8-iso prostaglandin $F_{2\alpha}$ (8-iso $PGF_{2\alpha}$) excreted in the urine. The compound measured, 8-iso $PGF_{2\alpha}$, is formed from free radical-mediated oxidation of arachidonic acid, a compound present in membranes of cells throughout the body. Investigators tracked the mean amplitude of glucose excursion (MAGE) to gauge glycemic instability; they also analyzed the area under the curve of postprandial (AUCpp) blood glucose spikes as well as A1C.

Monnier and colleagues conclude that levels of 8-iso $PGF_{2\alpha}$ correlate most strongly with MAGE ($r=0.86$; $P<0.001$), indicating that glycemic instability amplifies oxidative stress. Patients with type 2 diabetes had significantly higher rates of 8-iso $PGF_{2\alpha}$ secretion ($P<0.001$) than did non-diabetic case controls. Levels of 8-iso $PGF_{2\alpha}$ also correlated strongly with AUCpp ($r=0.55$; $P=0.009$), the indicator of postprandial excursions. Notably, the levels of 8-iso $PGF_{2\alpha}$ did not correlate with fasting plasma insulin, A1C, fasting plasma glucose, or mean daily glucose concentrations as indicated by continuous monitoring data. Univariate analysis was performed as well for body mass index, systolic and diastolic blood pressure, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and free fatty acids, and no relationship was found between 8-iso $PGF_{2\alpha}$ and any of those variables.

Of course, the study is limited by its small size and design, as it is cross-sectional and observational. The authors note, however, that the results of their study do open the door for other larger studies: " …because activation of oxidative stress is one of the main mechanisms that leads to diabetic complications, the present data open the field to conduct interventional studies aimed at treating glycemic disorders not only by reducing HbA1c and mean hyperglycemia but also by flattening acute glucose fluctuations." (page 1687). A logical question might be why this hasn't been studied more in the past; we understand oxidative stress has been difficult to measure previously and is obviously controversial, but we hope to see more studies that substantiate (or contradict) this exciting paper, one way or the other.

Drs. Michael Brownlee and Irl Hirsch, long-time champions of the importance of glycemic variability, wrote an editorial that accompanies this and Dr Saudek's (see below) paper on A1C – the editorial is titled "Glycemic Variability: A Hemoglobin A1C-Independent Risk Factor for Diabetic Complications." In addition to underscoring the significance of the article by the mere existence of an accompanying editorial in JAMA, the editorial ties in two key avenues of research. First, Brownlee and Hirsch note that the study corroborates the data from the DCCT that suggest that glycemic instability is an independent risk factor for diabetic complications; they note that *in patients at the same A1C*, risk of diabetic retinopathy was 50% more likely in the group with conventional control than it was in the group with intensive control.

Second, the editorial addresses the importance of prostacyclin synthetase, an anti-atherosclerotic enzyme that is inactivated by glycemic excursions. Dr. Brownlee's unpublished research shows that in

lean non-diabetic subjects, free radicals generated by deliberately-induced glycemic excursions cause a significant reduction in the activity of this enzyme, which prevents the initiation and progression of atherosclerosis. In a recent presentation, Dr. Brownlee said that the enzyme was shut off for 24 hours after one four-hour period with blood glucose above 180 mg/dL. As most people with diabetes, especially type 1 diabetes, experience post-prandial spikes above 180 mg/dL, this would suggest that in people with diabetes, this enzyme is rarely active. This effect of glycemic excursions is additional to the vascular oxidative damage induced by both chronic hyperglycemia and acute fluctuations in glucose.

In our view, Monnier's work represents some of the most important research recently carried out in diabetes. While the most definitive study of glycemic instability would be a DCCT-style outcomes study, such a study would be a massive and expensive undertaking – one we don't anticipate seeing, although we believe patients and industry would both ultimately benefit from such an undertaking. At any rate, as noted, oxidative stress has been conclusively named "one of the main causes of vascular disease" (page 1685). We believe this study could ultimately change the course of clinical practice, as it questions the principles that have been the foundation of diabetes therapy since the DCCT. It is not clear, for instance, that achieving normal fasting blood glucose followed by a postprandial spike—which is much of diabetes care today—will result in fewer complications than would sustained hyperglycemia. Indeed, the study found no correlation between fasting glucose and 8-iso $PGF_{2\alpha}$. It appears that clinicians need to be working to minimize glycemic instability as well as A1C. Saudek's paper (reviewed below) appears to suggest post-prandial testing is not clinically useful; we find the research on this front lacking on both sides. We understand there will be a paper coming up in Diabetes Care about 7-point testing in the DCCT – we don't think that is the right study to examine since the 7-point testing was done only once every three months (where the patients could train themselves to do especially well) but we'll wait to see what that piece looks like. We expect the responses to the paper will prompt the most interest and will prove the most intriguing.

Broadly speaking, we believe Monnier's findings have significant commercial implications for both diabetes drugs and devices, especially Byetta, Symlin, continuous glucose monitoring, and episodic monitoring. Minimizing glycemic instability will not be simple, but there are some products well positioned to aid in this effort. Byetta and Symlin, for instance, specifically minimize postprandial excursions, and we expect as research on this front accelerates and begins to affect clinical practice, use of both compounds will further expand. Providers and patients will seek continuous glucose monitoring—the technology which made Monnier's study possible—as a tool to gauge, anticipate, and hopefully prevent glucose peaks and valleys.

This study also may spur increased episodic glucose testing among type 2 patients as well as use of disposable pumps. In their editorial, Brownlee and Hirsch write that Monnier's "data suggest that in patients with type 2 diabetes, SMBG should be performed with increased frequency to monitor glycemic variability, regardless of the effect on HbA1c" (page 1708). That couldn't be more clear! The authors also suggest that new therapies should be geared toward minimizing these excursions and that current therapies should be evaluated for their impact in this area. It is also argued strongly and persuasively in this issue of JAMA that getting the numbers isn't enough – obvious though it may sound, patients need to know exactly what *to do* with the numbers – which, we think most HCPs would agree, they don't all. Various reasons exist but we would put lack of reimbursement for education at the top of the list – policy on this front needs changing asap! Finally, it is worth noting that in addition to reducing oxidative stress and complications, we believe that increasing glycemic stability will result in a higher quality of life and sense of well being for people with diabetes and in a reduction in severe hypoglycemia that often results from overcompensation for hyperglycemic spikes. Perhaps with increased attention to glycemic instability and innovation in this area, there will be some progress in stemming the astonishing rates of diabetic complications. We can only hope.

Saudek, Christopher, et al. "Assessing Glycemia in Diabetes Using Self-monitoring Blood Glucose and Hemoglobin A_{1C}." JAMA. 12 Apr 2006. 295(14):1688-1697.

In this clinical review, Drs. Christopher Saudek, Rachel Derr, and Rita Kalyani assess the evidence behind self-monitoring of blood glucose (SMBG) and hemoglobin A_{1C} (A1C) and make suggestions on their use. While SMBG and A1C both serve as measures of glycemia, they provide very different information. While SMBG measures the immediate, hour-to-hour blood glucose level, A1C measures long-term or month-to-month glycemia. After identifying reports relevant to SMBG and A1C from MEDLINE searches (1976-2005), Saudek et al. evaluated the underlying use of SBMG and A1C, cofounders and sources of error in each measure, and the clinical utility and controversies behind these measures.

SMBG findings:

- **SMBG allows patients to know their blood glucose level immediately and at any time**, thus allowing correlation of glucose levels with daily events and treatment regimens. As a result, SMBG has shifted some diabetes management responsibility from healthcare providers to the patient. For very motivated patients, we might suggest nearly all diabetes management has shifted.
- **The aged-adjusted percentage of adults with diabetes performing SMBG daily increased 22% between 1994 and 2003, from 36% to 58%.** Variability in intensity of treatment affects frequency of SMBG, and cost inhibits its use.
- **The cost of SMBG is enormous.** It is estimated that the Medicare B program spent over $460 million on SMBG in 2002, more than half of its Part B budget for the diabetes ICD-9 code.
- **Glucose meter results are generally not as accurate as laboratory measurements.** The International Organization for Standardization recommends that over 95% of readings be within 15 mg/dL for glucose readings <75mg/dL and within 20% for higher blood glucose levels, when compared with the standard YSI 2700 reference method. It is well known that meters do not always meet these accuracy standards. An interesting research question is what the accuracy looks like for current continuous monitors – we will continue to follow this question, which is not now conclusive.
- **Inaccuracies in glucose meter results are most often caused by patients, as opposed to being instrument-related.** Errors often caused by patients include: failure to calibrate the glucose meter regularly, improper use of control solutions, poor hand washing, and dirty meters. Storing test strips in conditions of excessive temperatures and humidity can cause overestimation of blood glucose levels. Certain drugs, including ascorbic acid, dopamine, acetaminophen, and mannitol, can cause inaccuracies in some meters. A low hematocrit causes meters to overestimate results, and glucose meters are less accurate in lower glycemic ranges and may overestimate blood glucose levels in high glycemic ranges. As is well accepted, checking alternate sites (such as the thigh or arm) during periods of frequent change may lead to false results after eating, exercising, or with insulin therapy.
- **In light of the cost of SMBG and the burden it puts on our health care system, it is important to evaluate the efficacy of SMBG in improving patient care.** While many studies have investigated this topic, Saudek et al. report that bias is very difficult to overcome in such studies. The larger, more recent trials that Saudek et al. reviewed support the conclusion that SMBG improves glycemia when the results are translated into action. Clearly, simply performing SMBG without acting upon the results is ineffective, and thus there must be an educational link to SMBG. This is, of course, where the reimbursement issue comes into play. It is worth noting that the benefits of SMBG are clearest among patients using insulin (they can actually "do something" in response to numbers, unlike other patients not on easy adjustable medication), while evidence is weaker for the effect of SMBG on glycemia in non-insulin-requiring type 2 diabetic patients.

Based on their findings, Saudek et al. make several recommendations on SMBG use. Most of these are very basic, but we also know many PCPs don't follow them.

- Patients should be taught how to act on their SMBG results and how to communicate results to a HCP, who should evaluate results and communicate to the patient treatment changes.

- Optimal frequency of SMBG should be decided by patients and clinicians on an individual basis, as no definitive clinical studies on optimal frequency have been conducted. The ADA recommends SMBG at least three times daily for patients with type 1 diabetes, while it does not give a frequency recommendation for patients with type 2 diabetes. Saudek et al. suggest more frequent SMBG among patients with more unstable glycemia, those prone to hypoglycemia, and while treatment changes are being made.
- Optimal timing of SMBG also remains uncertain. Monnier et al.—the authors of the glycemic variability study in this same issue of JAMA—have found that "extended post-lunch" blood glucose values predict A1C <7% better than fasting glucose, while a three-point daily testing system (8am, 10am, and 5pm) is best for type 2 diabetic patients with poorer glycemic control, and a four- to eight-point daily system was best for patients with type 1 diabetes. In their practices at Johns Hopkins, Saudek and colleagues usually rely on fasting, preprandial, and bedtime SBMG. They seem to have something against post-prandial testing, noting that evidence is "relatively small" – while there isn't evidence to guide away from post-prandial testing, Saudek just flatly says "… if the preprandial SMBG and A1c values are in a good range, there is little evidence to recommend testing after a meal." While we agree that perhaps if values are good, extra testing perhaps doesn't need to be advocated, we come back to the fact that two thirds of type 2 patients are over optimal A1C levels, and so it would have been more helpful to be able to discern Saudek's view on this front.
- In cases of diabetes during pregnancy—both for pregestational type 1 diabetes and gestational diabetes—postprandial SMBG has proven efficacy. Fertility has been established as an excellent motivator.
- Patients using insulin pumps should test frequently, both in order to guide bolus insulin dosing and in case insulin delivery is mistakenly interrupted. We aren't aware of studies that show how often pump patients actually do test, but we note our belief that pump use will increase with the advent of continuous – so a disproportionately higher percentage of users may be able to obtain them.
- New data management features available on glucose meters for calculating means, variance, and trends allow for the most effective use of SMBG, and Saudek et al. believe that this data management capability is "useful and underutilized." We found this odd – if he believes that variance should be used more frequently, we wonder how variance will be calculated, since he doesn't argue for more post-prandial testing – so we assume some variance scores could be determined, but we would guess they would guess they may be of limited use if there are not enough values tested.
- Big picture, we believe in the importance of post-prandial glucose reductions; if the reductions have been achieved (for example, with the help of Byetta or Symlin), then there may not be tremendous clinical use stemming from more post-prandial testing, especially if the testing conveys only very similar numbers.
- In the long-term future, SMBG may be replaced with continuous glucose monitoring systems and ultimately the development of a closed-loop insulin delivery system.

A1C findings and conclusions:

- **A1C serves as a measurement of average glycemia over the previous several months.** About 50% of A1C is determined by glycemia during the one month prior to measurement, 25% from the 30-60 days before the measurement, and 25% from the 60-120 days prior to the measurement.
- **Confounding conditions such as hemoglobin variants affect A1C test results**. Over 700 hemoglobin variants have been reported, most of which are clinically silent yet give rise to erroneous A1C results. Thus, a hemoglobin variant should be suspected if the A1C result is surprisingly high or low or varies widely between laboratory methods used. In such cases, Saudek et al. report that a boronate affinity chromatography method may be most reliable form of A1C measurement. Apart from hemoglobin variants, any condition that shortens erythrocyte lifespan—such as kidney disease, liver disease, and hemolytic anemia—lowers A1C. Meanwhile, iron-deficiency anemia is associated with elevated A1C, as is any condition that slows the process of erythropoesis, such as aplastic anemia.

- **Saudek et al. report that glycemic lability does not affect A1C.** They reached this conclusion by analyzing the standard deviation of blood glucose in patients performing frequent SMBG.
- **Because A1C has served as the primary measure of glycemia in the DCCT, UKPDS, and many other studies, the authors report that A1C is "the basis upon which glycemic control is known to be a mediator of diabetic complications."** Intensively-treated DCCT patients achieved a mean A1C reduction of 1.8%, which resulted in huge decreases in microalbuminurea, development of new retinopathy, and development of clinical neuropathy. EDIC, the long-term follow-up study to the DCCT, has also found a significantly lower risk of macrovascular complications among intensively-treated patients. Still, authors note (surprisingly) it is not clear whether regular A1C testing itself improves glycemia.
- **Evidence from randomized controlled trials indicates that point-of-care A1C testing may be more effective at lowering A1C levels than central laboratory testing.** Indeed, point-of-care testing allows HCPs to make immediate therapy changes while the patient is present.
- **Fructosamine and 1,5 anhydroglucitol (1,5-AG) are two additional long-term measurements of glycemia, although they are less widely used due, we believe, to poor reliability.** The FDA recently approved a measure of the 1,5-AG assay, which may serve as a useful measure of post-prandial hyperglycemia.

The authors make several recommendations on A1C use:

- **They report that there is no scientific basis for choosing a single A1C target.** The association between glycemic control and complications is continuous, yet the risk of hypoglycemia increases as A1C level decreases. Thus, "determining a glycemic target involves considering the individual risk-benefit ratio." As is well known, the ADA currently holds to an A1C target of <7%. However, certain patients, such as those prone to hypoglycemia unawareness, should use higher A1C targets.
- **Expert opinion, as expressed in the "Standards of Medical Care In Diabetes" (Diabetes Care, 2005), recommends A1C testing twice-yearly in patients meeting glycemic goals and quarterly in patients who are not meeting goals and when therapy has been changed.**
- **A1C testing is currently not accepted for purposes of screening or diagnosing diabetes.** However, the authors comment that A1C would serve as an easy laboratory test that does not require fasting and is not greatly affected by diet or activity level in the few days prior to the test. Moreover, improvements in assay standardization have improved sensitivity and specificity compared to standard oral glucose tolerance testing. One study found that the specificity for detecting undiagnosed diabetes was 97.4% for A1C results 2 standard deviations above the mean of 6.1% (Rohlfing CL, et al. *Diabetes Care.* 2000.)

The future of A1C testing appears to lie in the hands of the International Federation of Clinical Chemistry. Standardization of A1C methods has increased greatly over the last 25 years, and this study reports that 99% of laboratories in the U.S. currently use certified assays that are traceable to the DCCT glycohemoglobin reference, with a total imprecision of ≤4%. However, the International Federation of Clinical Chemistry has developed a new reference method for measuring glycated hemoglobin that is reportedly more specific than the current A1C method. The reference range for this new method is 1.3% to 1.5% lower than the current A1C values. Thus, instead of using a normal range of 4% to 6%, the new normal range would be about 2% to 4%. All values in the diabetic range would be about 2% lower than the values used currently, and a conversion equation has already been developed. The name of this new test has not yet been decided, yet "mean blood glucose equivalent" has been suggested. A concern is that new reference ranges, new targets, and a new name may throw patients off and even lead to a deterioration in patient glycemic control. However, if needed, there is always the option of converting the results to the currently used, familiar units. **We believe that diabetes treatment must be geared not only toward lowering A1C but also toward lowering glycemic excursions, especially in light of the report in this issue of JAMA on the association between glucose excursions and oxidative stress, independent of A1C (Monnier et al.).** In their conclusion, Saudek and colleagues report that "changes in

both approaches [SMBG and A1C] are ongoing but with proper control of glycemia, diabetes can be successfully managed." However, we question their evaluation of proper control of glycemia.

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

10. Upcoming Diabetes Conference Previews

- **Pediatric Academic Society, April 29-May 2, San Francisco, CA**

This meeting is happening as we write in San Francisco. The Pediatric Academic Societies meeting comprises many, many different tracks of almost every topic within pediatrics one could imagine. On the diabetes front, we'll be interested in the presentation by Dr. Mark Sperling of the Children's Hospital of Pittsburgh on neonatal diabetes, updates on Trial Net and STOPPT2D, the cleverly titled "Obesity Symposium—the BIG Picture," and a session on the treatment of metabolic syndrome in children. http://www.pas-meeting.org/

- **Morgan Stanley Unplugged**

This meeting is among the most interesting of all the investment conferences for two reasons: one, it is primarily run by the analysts, and two, it leverages something they identified long ago – free ranging conversations trumps pre-set comments, every time. For all, it's a boon – these conversations are webcast, unlike the breakout groups at most conferences that almost never are (except when companies insist on it). There are many, many companies we'll be interested to hear that have diabetes franchises – who knows what will be said about diabetes, but sometimes it is what isn't said that is most interesting! The list includes BMS, GSK, J&J, Alkermes, Nektar, Novo Nordisk, Amylin, and Roche.

- **Second Metabolic Diseases World Summit, May 18-21, Long Beach, CA**

This metabolic disease summit will have some world-class speakers, many from industry (J&J, Abbott, Amgen, Wyeth, Hoffmann-La Roche, Merck, Sanofi, Pfizer, DiObex, GSK, Lilly, Regeneron, Takeda) as well as some academic luminaries. In particular, we're very excited to hear Dr. Dan Einhorn of Scripps talk about "The Clinician and Metabolic Syndrome," since the area has been so controversial. ("*It doesn't exist." "Yes it does!" "No it doesn't!" "Well, it isn't clinically useful...." "What about...?")* http://www.gtcbio.com/hotal.asp?cid=17

- **American Diabetes Association, June 9-13, Washington DC**

Does the biggest meeting of the year even need an explanation? We would start by suggesting that you get your registration in if you have not done so already! Every ADA seems to get bigger and better, and this year promises to be no exception. We look for several new products to vie for the spotlight, including all the incretins, Pfizer's Exubera, DexCom's STS, and Medtronic's Sensor-Augmented Pump….

—by Erin M. Kane and Kelly L. Close

NEXT ISSUE: Diabetes Close Up #59: AACE meeting synthesis; Continuous Glucose Monitoring/Insulin Delivery synthesis; ADA preview. Stay tuned!