DIABETES CLOSE UP

Diabetes Close Up
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The Excitement called Byetta and the Inspiration of Dr. John Eng

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

From the Editor: It's been one of those months when there are so many intriguing elements of diabetes that I feel I have barely had time to catch my breath! Amylin's Byetta (the compound formerly known as exenatide) approval must be at the very top of the list. I keep having conversations with people about it – doctors, CDEs, patients, analysts, industry followers, corporate colleagues – it is fascinating. One (i.e., I) could talk for hours about the target market at present, how the target market will evolve, pricing, reimbursement, coverage, how the drug will be perceived and accepted by healthcare providers and payors, how important the positive side effect profile will be, how amazing it is that the FDA didn't require a panel meeting for this first-in-class compound, etc. Even my husband has joined in the fray. Byetta even came up at SFMOMA last weekend. I stepped away to buy my favorite Sol Lewitt postcards and when I returned to Café Museo, I heard my husband John talking to a museum-goer: "Oh, you can't have biscotti? You have diabetes? … How is your A1c … [digression, rumble, rumble, aside to me 'she doesn't know her A1c? How could that be? …'] … Well you should try Byetta. … [poke from me, huddle, whisper] …Oh, sorry, Kelly says – that's my wife, who has diabetes too, she'd love to talk to you, she always loves meeting patients – you should ask your healthcare provider about trying Byetta. … What's Byetta? Oh, it's the old exenatide … what's exenatide? [stage whisper, to me, 'she doesn't know what exenatide is? Haven't you been dwelling on this drug since Paris?] … I guess you haven't seen the news. This is a drug Kelly keeps talking about, it's very exciting. … Oh, no, she won't take it, but she writes about diabetes. … Yes. … You don't gain weight on it, in fact, you lose weight … that's the main thing. … Yes, yes, lose weight. … Yes, I know, but you can lose weight on it. I wish I could take it! No, no, I'm not diabetic, that's why I can eat this biscotti. … Oh, right, I know you [both] can eat biscotti too. … Anyway, there are scads of other reasons this medicine seems good. … What are they? Oh, well, no hypos [whisper from me, 'well at least in monotherapy {what's that}] and fewer hypos anyway] … Kelly gets too many hypos, I wish she could take it … Bye, we're going to see Bechtel and then photography…!"

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Is that so sweet, '…it's the old exenatide …'? ("Wasn't that right?" he asked … "Why do you think that's funny?") So yes, we are watching this unfold eagerly and intently.

In this issue:

- **Our view on Byetta's approval and our take on the top ten myths surrounding Byetta and Amylin:** Last month we asked if you could imagine a better combination than St. Patrick's Day and Symlin approval. Now, how about May Day and Amylin's Byetta approval?! On April 28, we kept going to www.exenatide.com – 11 p.m., midnight, 1 a.m.… When the press release came out a couple of hours later, information was posted at www.byetta.com. We think what this compound has the potential to do for patients is profound. Our take inside in the "longer version" includes our take on the label and the market and why we think healthcare providers and patients will warm to the drug. We also discuss Symlin, now out and in pharmacies.
- **Our interview with John Eng is item 6 in our "longer version" of DCU. Below, some excerpts from this moving conversation**:
  - **On being in endocrine:** *I estimate that 99% of research findings are not earthshaking or new, but every stone still has to be turned over. It's the remaining 1% where you might find something interesting or new. I think that's what I really learned from Ros (mentor and 1977 Nobel Prize Winner, Rosalyn S. Yalow)-- the motivation to continue the search without becoming discouraged ... She would challenge us in our weekly conferences by saying, "Think big thoughts. What have you learned?"*
  - **On what he thought at the time of discovery**: *Being a physician and doing research, a Holy Grail to is to make a discovery and bring that discovery from the bench to the bedside. Although I can't personally*

develop the discovery to the point where it is used at the bedside, the concept is to make a discovery that later develops into something clinically useful. It can't get any more gratifying than for that to happen.

- **On the fork in the road:** *Exendin-4 required patent protection before any pharmaceutical company would risk hundreds of millions of dollars to develop it. In the memo, the VA general counsel said, 'VA declines to patent,' but went on to say, 'You can patent it on your own.' Here I faced a fork in the road and like Yogi Berra I took it …*
- **On patenting**: *I'm a physician, a scientist, what do I know about patenting? On the other hand … I thought, "If I don't patent it no one will touch it."*
- **On the clinical path**: *It's [been] really thrilling to follow Exenatide's development. I'm an outsider because I'm not engaged in its development, but it's wonderful to see. … I see its development like that of a child. As your child develops you have great pride in the child. You send it off to higher levels of school where the child develops in larger environments. In my case, the child and the development were guided flawlessly.*
- **On the competitive landscape***: I'm a biased party. I am biased for Exenatide, and I hope it does better than competing agents. However, I also see things from a patient's point of view. With that in mind, really, what is best for the patient is, in the end, what counts. It won't be a single compound. It will be multiple compounds. With Exenatide, it's like software - there's a version 1, a version 2—so there will be evolution there too. LAR? Oh, I can't talk about that…*

The Longer Version

1. Amylin and Amylin's Byetta: Debunking the Top Ten Myths

So as everybody probably knows by now, Byetta was approved by the FDA on Thursday, April 28, just as expected, as the PDUFA date was Saturday, April 30. The Amylin investor conference call about the drug approval is on the corporate website, which is chockfull of information on the next steps for the drug (for more stellar information, check out their annual report, just posted on the website and highlighted in our annual report watch). One excellent thing about the call is that it started off with a big cheer from the management team, demonstrating their delight that this drug would now be available to patients. During my Wall Street research days, there were not very many spontaneous moments like that, or moments of pure glee. From a patient perspective, this was wonderful to behold. It reinforced for me that the company really is *all* about the patient, full stop. How great is that?!

So on the conference call for the approval, and then on the earnings call, and then at the Morgan Stanley conference, there seemed to be some undue skepticism about the drug and the company. We started counting off on a couple of fingers some myths – soon, we were at one hand, and then two hands. We stopped at ten, which we take some time below to discuss.

Myth #1: The label for Byetta isn't as strong as expected (stay with me ~ this is multiple-part).
Reality #1: The label is *stronger* than we expected. We think there are a number of sources for the confusion over the label.

- **It's just a word – approvable is a positive in this case!** Typically "approvable" is actually negative, because the FDA is saying that what was requested was not actually approved, though it is approv*able*. In this case, we can't imagine anyone would expect that the FDA would actually give outright approval to monotherapy, when only two 28-day studies were submitted. We think it's terrific that the agency said that Byetta could ultimately be approved as monotherapy. You know why? From an adoption perspective, it means the target audience is bigger, but in real life, the reason it's great is because patients could get on this valuable therapy earlier, and more broadly, just the notion of patients going on more aggressive therapy earlier could become more accepted. Type 2 is such a progressive disease and by the time patients go through the rigmarole of diet/exercise, metformin, SFUs, combination therapy … well, the years go by, weight is gained, fasting blood glucose levels rise, post-prandial levels rise, complications ensue. It seems likely to us, based on data, that those who go on Byetta will likely be healthier and lighter and less likely to experience complications (we know that it will be important to see more monotherapy data, but UKPDS did show that better A1Cs result in statistically significantly fewer microvascular complications and we are personally assuming you will see an A1C benefit, especially because these patients are often in very poor control right at the start). So given that we know that what's really expensive are *complications* from diabetes, the concerns over pricing (see below) are also overdone in our book because if you could treat first, and avoid complications, we'd all be better off – patients, because they'd be in better health, and everyone else, because fewer taxpayer dollars would be spent.
- **Byetta shouldn't be used to replace insulin. Of course not!** There was confusion over the label because in the *safety* section, it said Byetta should not be used to *replace* insulin. Right. That means if you have type 1 diabetes, i.e., you need insulin to survive, or if you have very advanced type 2, i.e., a burned out pancreas and you'll go into DKA if you don't take insulin, you shouldn't *quit* taking insulin and substitute Byetta. This is a fact, it's neither disappointing nor surprising. If more type 2 patients could take Byetta before they reach the burned out pancreas stage (which some reach while they are failing oral meds), we'd all be better off.
- **Lantus data isn't on the label – we would not have expected it to be.** The company has said that full Lantus data will be presented at the ADA. It's going to be fascinating to see how the two compare, particularly on the side effect front. What has been disclosed to date is really only top-line data, i.e., that both prompt about the same A1C change and that there's an eight-pound difference in weight change between the Byetta (down five pounds) and Lantus (up three pounds) groups. We should also expect to see the Lantus data published in a peer-reviewed within a reasonable timeframe – this was noted on the conference call. It's worth noting that publication results to date have been superb for

Byetta. One AMIGO trial published in *Diabetes Care* last November, and the other two in April; three AMIGO trials published in the main diabetes peer-reviewed journal – publication results don't get much better than this. Data is such an important factor for healthcare professionals, because it's the proof in the pudding (peer review isn't easy), it bolsters confidence, and is very important for education and for reimbursement. On balance: not a big deal that this Lantus data wasn't on the label, but expect that data on this front will prompt greater use of Byetta over time. Look at it this way, when the full Lantus data is released, it should get some good attention. Tangent – people have focused a lot on how big the failing oral drugs market is – but perhaps not necessarily on so much on other markets. We think there are countless other markets – combination therapy with TZDs, combination therapy with insulin, pre-diabetes therapy –with major potential and all markets in which we could ultimately, eventually, see Byetta in use.

- **More on monotherapy**: To reiterate, we know that diabetes is a progressive disease, and the average A1c for type 2 patients of 9.3[1] suggests that many people stay on the wrong therapy too long, including the infamous "diet and exercise" regimen (also known to some as doing nothing). It was interesting that at the Canadian Diabetes Meeting in 2003, when new, aggressive guidelines came out (see guidelines at http://www.diabetes.ca), it was actually discussed that for patients with an A1c over 9.0, insulin itself should be considered as a first-line therapy. This is great, but as we have written before, there is often resistance to insulin from both healthcare providers as well as patients. We think it's outstanding that there will now, with Byetta, be another option for patients failing oral therapies *before* moving to insulin. By the same token, we also think it would be terrific for patients to have a first-line therapy that is more efficacious than diet and exercise or multiple drugs, but that is simple to use and doesn't prompt hypoglycemia or weight gain.

Myth #2: The market for Byetta is limited because of the injection required.
Reality #2: Injections are so not that big a deal.

Okay, yes, all else equal, would you choose or not choose an injection? Well, all else equal, would you choose or not choose diabetes? The question in our view isn't whether using a pen to inject medicine is worse than a pill – it is – but it's really what the patient benefit/cost analysis is when all the information is examined. On balance, we think that there is definitely a segment of patients willing to inject in order to reap the benefits. Remember, they don't have to *love* it – they just need to be willing to consider the tradeoffs and to decide that the potential for significantly better control, fewer hypos, and reduced weight is worth it. We believe we'll see that benefits are meaningful enough for a sizable percentage to start and maintain the drug – so ultimately, while we agree that injections are a relative disadvantage, we don't think they come close to defining deal-breaker status for a good percentage of patients. Keep in mind that many of these patients have tried a lot of alternatives!

To boot, we believe that pen technology has improved and that actually, shots don't hurt that much, whether by pen or syringe (the gauge has really improved, which is relevant for Symlin, 'til it's available in a pen – Byetta is only in a pen). We think a *bigger* deal is the "failure" factor that often accompanies the move to insulin, i.e., many patients (and families) resist insulin because they associate it with failure. More on that below. This failure factor won't apply for Byetta, however, because unlike insulin, it's not considered and won't be perceived as "the end of the road" for patient therapy. By contrast, because this is a brand new class, there may even be benefit from a curiosity factor.

We think when patients resist shots – and for sure, some do – the resistance isn't necessarily about shots, per se, sometimes it's about insulin itself and how hard insulin *can* be to take for a host of factors. This is true for some, not everyone – we stress it is key to remember how broad a range of patients there are across the type 2 continuum. Ultimately, we believe many could use Byetta, but at the start, let's keep it limited to those failing oral therapy. Back on insulin - to boot, multiple other reasons exist why healthcare providers have historically resisted prescribing insulin – some of it is due to the complexity, some is due to hypoglycemia risk, some is due to hypoglycemia fear, some is due to weight gain. "*Weight gain*!" some scoff. "*What is two pounds or so* –

[1] Dr. Satish Garg gave this figure in his discussion of new insulin analogs at the recent Clinical Diabetes Technology meeting organized in San Francisco (April 15-16) by Dr. David Klonoff, which focused on continuous monitoring and insulin delivery strategies.

that's nothing!" Well, it's nothing except that over a decade, it's 20 pounds. Byetta will be taken by pen, and it's amazing what patients will do when motivated to improve therapy when weight gain isn't part of it – let's stay tuned on this front. By the way, some point to other therapeutic areas and note that patients resist shots, like in AIDS therapy. However, we think that's not comparing peaches to peaches. There, patients aren't used to taking shots and the injectable therapy isn't unique, as it is with Byetta. This is a new class! Plus, weight loss doesn't really figure in there, as it does with Byetta – right or wrong, certainly some segment of patients will do almost anything to lose weight.

One other thing about injections - pens are easier than vials and syringes. Europeans know this: in Europe, pen share is far higher than in the US – maybe 70-75% share versus 10-15% in the US. Pens are simpler to carry around, and the hassle factor is lower because fewer items are required – no alcohol swabs, no syringes, etc. We loved, by the way, the analogy of an insulin pen to a Mont Blanc pen on the conference call – we think that is apt, having seen a prototype of the new Lilly injection pen for Humalog Mix25 at Diabetes UK in April.

Myth #3: The price is too high.
Reality #3: The price is not too high!
The price of Byetta isn't *that* much more than the price of a TZD prescription, depending on dose, and we think it is justified given that it represents a novel therapy. $2000-$2100/year? Well, the average patient with diabetes spends $13,000-plus per year[2], and not because of drugs, because of complications. The standard deviation to that $13,000 must be pretty high – let's bring it down, along with the average. A great way to do that is for type 2 patients with A1Cs over 7 to go on more aggressive and/or better therapy earlier. The vast majority of the oft-cited $92 billion spent on direct costs of diabetes each year are associated with treating *complications* – drug costs are less than 15% of that total, inpatient costs exceed a whopping 44%. If we increased the average drug/monitoring costs per PWD and more patients treated their diabetes more aggressively and earlier, we feel confident the percentage of patients with complications would come down, the number of patients receiving inpatient care would also be reduced and the total costs would come down. Families would be happier, so would patients, and so would taxpayers. And there's argument because a pen is $172 rather than $122? Come, now! That's just $600 more per year.

Myth #4: Byetta's reimbursement challenges are too large.
Reality #4: Reimbursement will happen.
Amylin COO Dan Bradbury spoke directly to this point on the Morgan Stanley Unplugged conference call, at least with regard to Symlin, which I think we can extrapolate – he said that Symlin reimbursement was coming along rapidly (after two weeks in the market – impressive) and that the majority of plans were making Symlin available. What I know is that were I in charge of a health plan and patients were asking for Symlin, I wouldn't have a hope of saying no and retaining all the patients and I wouldn't be able to justify not reimbursing Byetta if I were already reimbursing Symlin. They are both new therapy for which there are no substitutes. As a plan, I think you sort of have to make first in class available, otherwise, you risk angering way too many people. If the drug is for a few months use, maybe not such a big deal, but the chronic disease lobby is big and getting bigger, particularly diabetes (new CDC stats show that there were 1.3 million more patients with diabetes diagnosed just last *year*, for example.) Indeed, the diabetes lobby is powerful – even if you don't have diabetes, someone in your family might, a co-worker might, or you just may have seen commercials. TZDs get reimbursed, there's no reason Byetta shouldn't. Now, we DO need to be patient while all the education filters up, but we can be patient – think about how long we've waited for Symlin itself.

Myth #5: Byetta will require too massive an education investment on the healthcare provider front.
Reality #5: Actually Byetta is relatively easy to learn, BUT certainly a big education investment is smart because it's a novel therapy and the more it's understood the better. However, once healthcare professionals get it, they'll get it, and the investment, which is big (and which we've been told for some time is big so no surprises here either) will have a stellar ROI, even if we won't necessarily see it right away.

It is going to take a lot of effort to reach 60,000-plus doctors and scores of CDEs and pharmacists and other healthcare professionals to tell them about Byetta and it shouldn't be expected to happen instantly. There is no

[2] http://www.diabetes.org/diabetes-statistics/cost-of-diabetes-in-us.jsp

magic pill that will teach them all about the benefits of Byetta though many of you could probably recite them back to front, which should underscore something about the quality of the benefits and the level of complication.

Ultimately, Byetta should be easy to teach to healthcare providers and to patients – this is a big deal. Insulin actually isn't that hard to teach either, but it has way more pieces – to teach insulin, you need to teach 1) the difference between basal and bolus; 2) carb counting if patients don't know it (they often don't if they aren't taking insulin); 3) insulin sensitivity factor (how much one unit of insulin reduces blood glucose); 4) insulin-to-carb ratio (how many carbs can be covered by one unit of insulin, which can be different throughout the day); 5) how insulin impacts exercise and vice-versa; 6) how meal composition and glycemic index impact blood glucose control; 7) what to do in the event of hypoglycemia – and that's just a start! Most endos acknowledge that moving patients to prandial insulin is one of the most complex elements of diabetes therapy because it is really hard to teach the pieces above – they aren't just easy facts to learn, they're very variable by person.

To teach Byetta, by contrast, 1) patients don't need to understand basal/bolus therapy; 2) they don't need to count carbs; 3) insulin sensitivity is a non factor; 4) insulin to carb ratio is a non factor; and 5) exercise should be able to be covered more easily; 6) meal composition and glycemic index are pretty much non-factors, or even positive factors, since satiety seems to improve with Byetta; 7) hypoglycemia is rare, and usually happens only with SFUs, and patients who are trained in SFUs probably already know how to deal with it (although if they are moving to insulin, different training is required). While basal dosing, which is the "background" insulin, typically becomes fixed following titration, prandial dosing can be quite variable and can be a hassle both for HCPs and patients. Before taking prandial (mealtime) insulin, one really needs to go through the elements above and multiple calculations per dose, every time a shot is taken, as shown in Table 1 (if you would like to see the excel sheet with formulas, e-mail us at info@closeconcerns.com).

Calculations required before taking insulin bolus - Case Study

Current blood glucose level	226
Target blood glucose level	100
Carbs in lunch	46
Insulin/carb lunch ratio	1:11
Insulin sensitivity	39
(number of points BG will drop per 1 unit of insulin)	
Number of points needed to drop to get to target	126
Insulin required to drop to target	3.2
Insulin required to cover lunch carbs	4.2
Total insulin dose required	7.4

This assumes there is no "unused insulin" in the system - if insulin had been taken in last four hours, this would also need to be calculated.

Source: ADA, John Walsh, Ruth Roberts, *Pumping Insulin: Everything You Need To Know for Success with an Insulin Pump*

It's worth noting explicitly that we foresee fixed dosing as a *major* advantage. Fixed dosing means Byetta will be easier for patients to take but also, probably more importantly, it will be easy to teach and to follow. Endocrinologists and CDEs have typically not had problems teaching dosing for insulin, but they have limitations on how much time they can spend with patients and teaching insulin dosing is never particularly straightforward. For what they are reimbursed, the level of commitment is typically VAST. PCPs have even less time to spend with patients teaching dosing algorithms than do endos/CDEs, especially on ten minutes a visit – while one option is to just refer to an endo for insulin, do you think the patient ever returns? There was an excellent moment at one of last year's ADA symposia in Orlando, where PCPs were on the stage in a "crossfire" with CDEs and PCPs were being urged to use CDEs and it was such a no-brainer, until one CDE pointed out that once the PCPs refer, the patient usually doesn't return. "*Why would they, if they come in with a 10 A1C and we get them to 7? We can prescribe statins just as well as they do, beta blockers too, but they just don't have time to teach insulin the same way we do given our ridiculous reimbursement system and they definitely don't want to deal with hypos…*". A basal insulin analog, e.g., Lantus, is typically not as hard to teach because dosage tends not to change much (although many will say "and because it's taken only once a day" we're not noting that, because we understand there's a growing trend for patients to take Lantus twice a

day; Levemir, Novo's answer to Lantus, will be prescribed as a twice-daily insulin), but prandial insulin – i.e., mealtime insulin – is harder to teach due to factors noted above. Of course, not every patient necessarily does all these calculations before eating – but they should, in order to get the right dose. Can you imagine recommending a patient go onto insulin and teaching them all this in 10-15 minutes?! No wonder Lantus has been so popular. However, we keep in mind that Lantus covers the basal insulin needs only, not prandial needs. Prandial insulin tends to be more complicated to teach and complicated to learn. Now if someone needs insulin, he or she *needs* insulin – but what if a PCP can prescribe Byetta and put off the need for insulin? Well, we know what we would do.

One final element of the Byetta simplicity is that no extra glucose monitoring is required. This is yet another element of care some patients resist, and it's great that the label doesn't require any extra monitoring, because it's one less item on which patients can push back. Importantly, Amylin CEO Ginger Graham did emphasize on the call that the company certainly was not discouraging monitoring or suggesting that patients do anything less than what is in their best interests. We loved that – monitoring is important so that patients know *how* they are doing. That said, particularly since Byetta's action is glycemia-dependent, we would expect to see less hypoglycemia than one would see with insulin or many of the oral drugs. And hypoglycemia is often what prompts the need to monitor, since when hypoglycemia ensues, a hyperglycemia-hypoglycemia rebound cycle often ensues.

Myth #6: It's really hard to get the attention of primary care doctors – how will they have time to consider Byetta?
Reality #6: Patient retention tool, hurrah! It's really hard to get the attention of primary care doctors for good reason: they are really amazing and really busy and always at risk to lose patients. For that reason, in our view, in time, PCPs will be all over Byetta because it'll be a retention tool for out-of-control patients. They may need to be won over, but that's fine, there's plenty of fodder. For primary care physicians, easier is better, all else equal. Importantly, Byetta could be a boon for PCPs because it offers them a way to *retain* diabetes patients who are not at goal and to improve their outcomes – ta-da!

As noted, PCPs don't have the time for complex therapy. Just dealing with blood pressure and lipids can often take up the entire ten minutes! A complicated therapy is tough because they don't have time to take patients through it and some patients actually leave because they don't want to deal with it. Complicated therapy is a challenge because PCP's often need to refer patients who need complex therapy (i.e., insulin) and often in doing so, they lose the patient.

Primary care patients are often struggling to lose weight – PCPs may wind up the heroes for prescribing a therapy that prompts weight loss – we'll wait and see on this front but we're curious because we have talked to PCPs who say they resist prescribing a therapy that prompts weight gain because the patients don't return.

At the 2nd International DAWN[3] Summit (November 2003), it was emphasized that one of the most potent barriers to migrating to insulin therapy by patients was providers' own emotional resistance. Some health care providers even admitted to using insulin therapy as a punishment, which in our opinion, reinforces patients' association of insulin with failure. We also believe that fear of hypoglycemia and the failure to understand insulin dosing represent other reasons for resistance, although this was not part of the DAWN study, which focuses on emotional well-being. This is actually a reason why we think some patients will agree to inject Byetta. One final element – look at Lantus! Lantus has been a success by any measure. We think it is actually overused because some patients that should be on prandial insulin try to get by on basal insulin only, using Lantus. That's another story for another day, but we mention it because the success has to do with the simplicity (see more below).

Myth #7: Byetta's side effect profile will severely limit uptake.
Reality #7: Byetta's side effects can be addressed. Side effects for other diabetes medications, including medformin, SFUs, TZDs, and insulin, are not trivial.

[3] Diabetes, Attitudes, Wishes and Needs study, which Novo Nordisk launched in 1998 – see http://www.dawnstudy.com

Byetta is associated with nausea, so patients should start at a lower dose. Usually the nausea is dose-related. I love how in these discussions, the implications always seem to be that except for Byetta (oh, and Symlin), side effects are never experienced!? Please! How many people experience side effects with Metformin? SFU's? TZDs? Side effects aren't a positive but they shouldn't represent a major show-stopper by any stretch. Keep in mind side effects are unfortunately sort of common[4], as our footnote shows – 53% of patients on metformin experience diarrhea, 26% nausea, and so forth.

Myth #8: Byetta needs to be refrigerated.
Reality #8: Keeping Byetta cold is probably not such a big deal. First of all, it's certainly possible that some patients will eat breakfast and dinner at home every night so they can just leave it in the shelf in the fridge behind the June Taylor marmalade. But who wants to rely on that! What's super easy is just to order a Frio; this is a little black pack that you fill with water every five days, then you stick the pen inside (or insulin vial and syringe) and go off and live your life – a very easy solution. http://www.frio.com. For what it is worth, plenty of people never refrigerate insulin but *also* never leave it on the dashboard in Tucson or in the car in Aspen and these patients are just fine, even though technically they are in violation of instructions to refrigerate. If you want to read more about this, go to a commentary by Dr. Nathanial G. Clark in Diabetes Care, Sept. 2003 – you can see the full text of the article at the following link:
http://www.findarticles.com/p/articles/mi_m0CUH/is_9_26/ai_107928442. Part of the piece reads: "*I set out to*

[4] From glucophage.com (metformin): 53% of patients in the treated group (n=141) of a placebo-controlled study experienced diarrhea and 26% experienced nausea (12% and 8% of the placebo group experienced these problems). Before going generic, metformin was a billion-dollar-plus drug. Medicinenet.com notes that the most common side effects with metformin are nausea, vomiting, gas, bloating, diarrhea, and loss of appetite. These symptoms occur in one out of every three patients. A serious--though rare--side effect of metformin is lactic acidosis. Lactic acidosis occurs in one out of every 30,000 patients and is fatal in 50% of cases.
From Actos.com: The most common side effects reported by people taking ACTOS included symptoms of upper respiratory tract infection, headache, sinusitis, muscle soreness, tooth disorder, and sore throat. Occasionally, blood glucose levels increased during clinical trials. As with other insulin sensitizers, weight gain may occur. In addition, mild to moderate swelling (edema) and a decrease in blood count (anemia) may occur. Low blood glucose was observed in a few patients who took ACTOS along with insulin or with other oral diabetes medications such as sulfonylureas.
From Avandia.com: The most common side effects reported by people taking *Avandia* were upper respiratory infection (cold-like symptoms) and headache. When taking *Avandia* with sulfonylureas or insulin, patients may be at increased risk for low blood sugar. Ask your doctor whether you need to lower your sulfonylurea or insulin dose. Some people may experience tiredness, weight gain or swelling with *Avandia*. *Avandia* may cause fluid retention or swelling which could lead to or worsen heart failure, so you should tell your doctor if you have a history of these conditions. If you experience an unusually rapid increase in weight, swelling or shortness of breath while taking *Avandia*, talk to your doctor immediately. In combination with insulin, *Avandia* may increase the risk of other heart problems. Ask your doctor about important symptoms and if the combination continues to work for you. *Avandia* is not for everyone. *Avandia* is not recommended for patients with severe heart failure or active liver disease. Also, blood tests to check for serious liver problems should be conducted before and during therapy.
From prandin.com: As with any blood-glucose lowering medication, hypoglycemia (low blood glucose) can occur … In clinical trials, the most common adverse events leading to discontinuation of Prandin therapy were hyperglycemia, hypoglycemia, and related symptoms. The most common other side effects reported were cold- and flu-like symptoms, headache, diarrhea, joint ache, and back pain.
From Lantus.com: possible side effects may include blood sugar levels that are too low (hypoglycemia); injection site reactions, including changes in fat tissue at the injection site; itching and rash; and allergic reactions. Hypoglycemia is the most common adverse effect of insulin, including LANTUS. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes. Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, timing of dosing, manufacturer, type (e.g., regular, NPH, or insulin analogs), species (animal, human), or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage. Concomitant oral antidiabetes treatment may need to be adjusted. … LANTUS is not intended for intravenous administration. The prolonged duration of activity of insulin glargine is dependent on injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia … Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy. An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes long-term and life-threatening hypoglycemia. Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid reoccurrence of hypoglycemia.

review the available literature on insulin storage. Lilly recommends using an opened bottle of Humulin R for 4 weeks, Humalog for 4 weeks, and Humulin N for only 1 week, whether refrigerated or at room temperature. Humalog Mix 75/25, Humulin 70/ 30, and Humulin N cartridges can be used for 7-10 days. Novo Nordisk states that vials or cartridges of Novolog can be used for 28 days at room temperature but says nothing about how long it will last if refrigerated. In a private communication from a staff pharmacist at Novo Nordisk, I received the following message: "*If human insulin vials that are stored under refrigeration are used beyond 30 days, the stability of human insulin vials is dependent upon a number of factors in addition to temperature. These factors include the number of injections per day, volume of insulin remaining in the vial, exposure to light, agitation, and technique used for dose preparation. The impact of these factors is difficult to measure and the health professional should advise patients on an individual basis concerning long-term storage of opened insulin vials when refrigerated*." Note that even though the label of Lantus explicitly says that it should be stored in a refrigerator at a temperature of 36-46 degrees Fahrenheit, Aventis itself wrote in a response to this commentary published in the same issue of *Diabetes Care*, "If refrigeration is not possible, the open vial in use can be kept unrefrigerated for up to 28 days in a place away from direct heat and light, as long as the temperature is not over 86 degrees Fahrenheit."

Myth #9: The competition is a major worry.
Reality #9: That's the thing with first-in-class drugs like Byetta – there is no real competition right now in terms of other GLP-1 compounds/other 1st in class drugs, and when they do emerge, the market will be large enough to support more than one player. Also, none of the competitive compounds have *all* the same advantages, i.e., restoration of first-phase insulin response (this is really important in our view), weight loss, glycemic-dependency, etc. If LAR is approved, the company may also have the playing field to themselves once again – but the main thing, we don't think that's so important.

This is what I don't really understand. A number of competitive compounds have been delayed or received other negative news, but Amylin never gets credit, quote unquote, for this, but worry over the competition appears to be extremely real. GLP-1 compounds have been delayed, as have PPARs. We have written about these drugs before in DCU; see, for example, http://www.closeconcerns.com/dcu/V3-9%20-%20Diabetes%20Close%20Up.pdf, which covers new drugs in development for type 2 diabetes. A number of these drugs have experienced delays (Liraglutide, CJC 1131, the entire dual PPAR-agonist class, etc.) and none of them have the stellar combination of advantages as does Byetta, e.g., restoration of first-phase insulin response (this is really important in our view), weight loss, glycemic-dependency, etc. On balance, that is positive for Amylin. One drug that is actually proceeding along apace seems to be Sanofi-Aventis' Rimonabant, which should be a great obesity agent. Right now, Byetta is not indicated for obesity, although we've definitely heard it discussed as such. Stay tuned, and get away from the thoughts that the competition is going to kill Byetta – there's just no evidence for this. For us, it's not so much about stealing market share, it's more about how big the pie expands – but we strongly suspect there'll be plenty of room for more than one great compound. LAR? We won't even mention it at this juncture.

Myth #10: Revenue expectations are already high so there is no upside.
Reality #10: You've got me on this one. Expectations *are* high for Byetta, at least some of them – it's a big range, and maybe the company won't beat all the high estimates, but it certainly seems in good shape to meet many of them – and high expectations don't mean zero upside. It's clear to me that Amylin is making a major investment in education for Byetta and Symlin, so we shouldn't expect sales to be so high right out of the block – this is a slow build. Let's look at Lantus for comparison. Here are the rough worldwide sales numbers: 2000[5]: $10 million; 2001: $85 million; 2002: $290 million; 2003: $550 million; 2004: $1 billion. Because it took Lantus until its third full year on the market to reach half a billion dollars in sales, I think it's probably reasonable to perceive the couple of revenue estimates for Amylin that exceed a half a billion in 2006 as aggressive by most normal people. By the same token, there are also long-term estimates for Symlin that get at least a tiny double take from us: $30 million in 2007? You can say that assumes about 15,000 people (conservative pricing assumption) taking the drug - a bit more than one percent of those with type 1 diabetes, but two to three percent of those on insulin. Ultimately, I tend to believe there is upside for Amylin, even with starts that aren't especially aggressive (they shouldn't be, this is about the end game, not the first few quarters). With a few exceptions, it seems like models are conservative in the out years. Longer term, there's real upside,

[5] Approval occurred in April, and the launch took place later in the year.

obviously particularly with LAR and especially when profitability ensues. Although it's true the projections span a broad continuum, and that competition will enter, we believe that Byetta and Symlin will prove good drugs - pricing is fair, reimbursement should be straightforward (they're novel, after all), and patient and provider acceptance will ultimately be strong, we believe. That last item is important on the patient side in particular: patients have become smarter and smarter and above all; it's them and their families that shouldn't be discounted!

We're already at #10 and we never even got to talk about the Symlin myths! The main one is that Symlin will never take off – if we had unlimited time and you had unlimited paper, we would go into why we like the drug, why hyper-intensively managed type 1 patients are talking about it, and why we wouldn't discount it, but also why we think it'll have a reasonably slow build as well.

– by Kelly L. Close

Commercial – Detailed Gut Hormone Report Offered. If you are interested in this topic, you can purchase a report on our website that we wrote in early 2004 that covers the ADA conference "*Research Symposium on the Novel Roles of GI Hormones in Energy Homeostasis, Obesity, and Diabetes*." This ADA conference was sponsored by Amylin Pharmaceuticals, Eli Lilly and Company, Novartis Pharmaceuticals Corporation, and Novo Nordisk Pharmaceuticals, and took place in Long Beach, CA, December 9-12, 2003. Approximately 150 doctors, scientists, and industry participants gathered at this series of sessions to discuss the role of GI hormones in diabetes, obesity, and energy homeostasis – this was before the compounds were getting quite as much airtime as they are today, and it was a very interesting session that helped me understand the science and the continuum better. See the www.closeconcerns.com (close concerns homepage) and click on reports for more information.

2. An interview with John Eng of the Veterans Administration Medical Center in the Bronx, who discovered Exendin-4.

John Eng discovered Exenatide (exendin-4), which was developed by Amylin and Lilly and received FDA approval April 29, 2005. It is now known as Byetta. Recently, we had the opportunity to sit down with John to talk to him about the events leading up to the exendin-4 discovery. John, who has spent his career at the Veterans Administration Medical Center in the Bronx, New York and is now Director of Clinical Informatics there, spent a generous couple of hours with us. The following are his comments on a range of topics:

On being in endocrine: I'm a physician. I trained in internal medicine and clinical endocrinology and wanted to do endocrine research. I started out in Rosalyn S. Yalow's lab at the Bronx VA and worked in her lab for the next 18 years until she retired. I learned that it is important to have a mentor in science. She was a wonderful mentor… She considered all of us, her fellows, as her scientific children. What I learned from her is not so much technical skills but rather a frame of mind to be persistent and tough during the search. Research is highly refined searching; search is after all part of the word research; and it's an endless search. As Thomas Edison said, science is 99% perspiration. I estimate that 99% of research findings are not earthshaking or new, but every stone still has to be turned over. It's the remaining 1% where you might find something interesting or new. I think that's what I really learned from Ros, the motivation to continue the search without becoming discouraged… She would challenge us in our weekly conferences by saying, "Think big thoughts. What have you learned?"

On one step forward and finding new hormones: "*Okay, I'm going to take one small step forward*" – in science there is a fair amount of that. There is a necessity to publish papers. Very often, the publications are small increments rather than really challenging discoveries, so it's important to encourage young people – like me, at the time – to think beyond science by smallest acceptable increments--to think big. My big thought was to say, "Since we deal with hormones in endocrinology, are there any new ones to be found?" I thought there *are* new hormones to be found.

About the time when I started working in Ros Yalow's lab, a group in Sweden at the Karolinska Institute published, what to me were, very exciting papers. They described a new way to look for peptide hormones. Their line of thinking was this: peptide hormones often have certain chemical characteristics. If you look for those chemical characteristics you'll find hormone candidates. It doesn't assure you they are hormones, but the presence of those

chemical characteristics greatly increased their chances. Victor Mutt and Kazuhiko Tatemoto in the Karolinska group purified, isolated, and published papers on a number of new hormones from both the intestine and the brain.

It turns out that there's a commonality between hormones in the intestine and hormones in the brain, which has been called the brain-gut axis. Why is that? No one has really come up with a universal theory, but it's been known for many years now.

The Karolinska group proved their concept by isolating new hormone candidates. In fact, one of the peptides they discovered is PYY, one that Amylin itself is hoping to develop.

The tool they used to isolate peptides is called a chemical assay. Ros Yalow was awarded the Nobel Prize in 1977 for discovering radioimmunoassay. However, radioimmunoassay will only detect what it was created originally to detect, unlike chemical assays, so the likelihood of finding something new by radioimmunoassay is small.

But chemical assay opened up the possibility of finding new things. In fact, Mutt and Tatemoto demonstrated that it can be used to find new hormones… They isolated a number of new peptides with unique chemical signatures. They were then faced with the need to prove the peptides are hormonal in nature – that's one of the anticipated requirements if I were to use a chemical assay.

I said, "I think there are new hormones. I'm going to look for them with a chemical assay."

[Interjection from Kelly Close] *Wow, that's a big thought*!

Well, yeah! Ros said, "Think big thoughts," but the corollary to that is the bigger your thoughts the harder you have to work!

Peptides are chains of amino acids. One end is the amino end, and the other is the carboxy end. Or in other terms, the N-terminal and the C-terminal part of the peptide chain.

Mutt and Tatemoto looked at the C-terminal part for C-terminal amide as a chemical signature. They had a well-developed assay, and it didn't make sense for me to try to emulate them.

So I looked at the other end of the peptide, the N-terminal end. It turns out that there are many gut and pancreatic hormones that have the amino acid histidine at the N-terminus or the very first position of the peptide chain. Classical hormones like glucagon, VIP, secretin, all have histidine at the one position. So I said, "Hmm, that's a good signal for a chemical assay."

I set up an assay to look for histidine at the one position of peptides. The first radioimmunoassay that she [Ros Yalow] made with Solomon Berson was an assay for insulin. They found that in the guinea pig, insulin was very poorly detected by their assays… How to explain that? Either guinea pigs had little insulin or the guinea pigs actually had as much insulin as any other animal but their insulin was different enough that it reacted poorly in the assay, which turned out to be the case.

The second immunoassay developed was against glucagon. In the chinchilla, radioimmunoassay couldn't detect any chinchilla glucagon at all. So you say, "Why chinchilla?"

Chinchillas are in the hystricomorph family, of which the guinea pig is also a member. We were interested in characterizing chinchilla glucagon. So we made a trip to a chinchilla farm [in Pennsylvania] and came back with chinchilla pancreases. I went through the usual steps: frozen pancreas is extracted by an alcohol and acid mixture, and assayed. Assay with a glucagon radioimmunoassay detected nothing. Nothing!

That raised the question: "Are chinchillas special?" Do they have no glucagon even though all known animals, mammals, and vertebrates have glucagon? Or is it their glucagon is sufficiently different in amino acid structure that the radioimmunoassay just couldn't detect it?

At that point I said, "I have this His1 assay," which is a chemical assay to look for histidine at the first position of the peptide chain. I applied it, and I found a fair amount of His1, the chemical signature… I used the assay to purify the peptide from the pancreatic extracts. At the very end, there was a single purified peak of peptide containing the His1 chemical signature. I sequenced the peptide, and sure enough, it was very close to human glucagon but not identical in sequence. There were amino acid differences, [which] explained why the glucagon radioimmunoassay could not detect it.

On confidence: The fact that this peptide sequence had some homology to glucagon gave me …*confidence* that I was on the right track.

I wanted to further validate this His1 assay with a more difficult test. I looked at a biological substance that I knew beforehand contained a His1-containing peptide but not in such great abundance that it would be a challenge to detect and purify. The reason for this added challenge is new hormones might be present in very low abundance; if they are, I would need a very sensitive chemical assay.

Around that time – so many years ago I forget which year it was – a report came out of the NIH in Jerry Gardner's group, which is a GI group. They had noticed reports that…when animals or humans are envenomated sometimes pancreatitis develops. Being a GI group, they were interested what can cause pancreatitis. They screened a wide variety of venoms to look for compounds in venom that can stimulate the pancreas because one way to produce pancreatitis is by *over-stimulating* the pancreas.

Drum roll! On the Gila monster: They found activity in the venom of the Gila monster lizard that stimulated the pancreas.

Gila monsters are kept in serpentariums, a kind of farm, along with different venomous snakes. They are milked for their venom, which is then dried. People purchase the venom to create anti-venom.

If any of us were hiking out in the desert and got bitten by a snake we would go to a hospital, and they would administer anti-venom, which is antibody created to the venom, to neutralize the venom now circulating from the bite.

The NIH group screened venom from a variety of venomous reptiles, one of which was the Gila monster. I read their report and thought, "Wow, that's great." They named the peptide they found in Gila monster venom helospectin, based on the Gila monster's scientific name, Heloderma suspectum. Helospectin has a histidine at the 1 position.

I ordered some Gila monster venom and put it into solution, because it comes in dried form, and assayed it. There was a lot of His1 activity by my chemical assay. I put it through the first purification step and observed two peaks, one of which was huge. The other one was very small. Looking at the pattern I said, "That's what I expect," because when you purify any peptide you'll get a large peak of purified peptide and a much smaller peak of degraded peptide. We always see that; it's very common. I said, "Clearly this major peak is helospectin and the minor peak, this small smidgeon peak, is degradation product."

I went ahead and sequenced both peaks. It turns out that the very small peak was helospectin, but the major peak, when I sequenced it, was not helospectin. It gave a sequence never described before. But it did have a histidine at the 1 position.

When you find something new, you have to name it. I named this peptide Exendin. There are two different poisonous lizards. One is entirely black and lives mostly in Mexico. Its scientific name is *Heloderma horridum.*

The other Gila monster lizard lives in the American Southwest. It's banded. It's actually very nice-looking. It has orange bands around the body. Its scientific name is *Heloderma suspectum*. The peptide I isolated from *Heloderma horridum* I named exendin-3 and the peptide from *Heloderma suspectum* I named exendin-4.

On exendin-4 and where it is: There was a very interesting coincidence. A person who worked at the NIH on isolating the earlier peptide, helospectin, was Jean-Pierre Raufman, a gastroenterologist. By that time he was

working at the Downstate Medical School. I called him to say, "Hey, I found this peptide." In talking with him, I said, "I'm naming this peptide Exendin…." but, since the first peptide from the Gila monster was helospectin, *that* can be considered exendin-1. Because a Belgian group found a peptide corresponding to helospectin in the other Gila monster species, *it* can be considered exendin-2. That's how I called the peptides that I isolated exendin-3 and exendin-4.

The name Exendin is actually very descriptive and practical. Basically, the venom secretion, which they now say is really a salivary secretion, is from an exocrine gland… Fluid flows to the outside of the body instead of into the bloodstream, so it's an exocrine secretion that has endocrine function. Exocrine secretion with endocrine activity gives the name Exendin.

On what he thought at the time of discovery: Being a physician and doing research, a Holy Grail to is to make a discovery and bring that discovery from the bench to the bedside. Although I can't personally develop the discovery to the point where it is used at the bedside, the concept is to make a discovery that later develops into something clinically useful. It can't get any more gratifying than for that to happen.

On what he thought at the time of naming: The next step that had to be taken was to show it had biological activity. Otherwise, it's just another peptide.

On timing and when exendin-4 was discovered: Exendin-4 was officially discovered in 1990. The first paper on exendin-3 was published that same year. Then the paper on exendin-4 came out two years later, in 1992.

On the next question: Peptides act on receptors. At this point, the question was: Does exendin-4 act on a receptor such as the glucagons receptor, the VIP receptor, the GLP-1 receptor, or some other receptor? Experiments showed that both peptides, exendin-3 from *Heloderma horridum* and exendin-4 from *Heloderma suspectum*, can act on the GLP-1 receptor. A difference between exendin-3 and exendin-4 is that exendin-3 also had a small amount of VIP activity, whereas both exendin-3 and exendin-4 act only on the GLP-1 receptor.

That is why exendin-4 was selected for development and not exendin-3, because of this additional activity of exendin-3.

[query from Kelly Close] *And when was it actually selected for development*?

That would be getting ahead of ourselves. I had just named it, and with Jean-Pierre Raufman, we found that it acts on the GLP-1 receptor. Then the question is, what's so important about GLP-1? A scientist named Joel Habener at the Massachusetts General Hospital found GLP-1 to have a very unique, very valuable activity. GLP-1, like many hormones, is known to stimulate insulin secretion, but what was really unique about GLP-1 is it stimulates insulin secretion only in the presence of a high glucose level. Glucose dependent stimulation of insulin secretion is very desirable. What was not known at the time, but it became quickly known, was GLP-1 gets degraded quickly in the bloodstream. The bloodstream has enzymes that cleave GLP-1 into an inactive form. The first two amino acids are clipped off rendering it inactive.

On DPP-IV: DPP4 stands for dipeptidyl peptidase, type 4, which cleaves off the first two amino acids rendering GLP-1 inactive. If you inhibit this enzyme you will extend the lifetime of the endogenous—our own GLP1 secretion thereby making it active longer. That's the basis for these new products that are being developed by other pharmaceutical companies.

On what else is being inhibited: I'm not knowledgeable about the science behind dipeptidyl peptidase enzymes. GLP-1 would have been the ideal therapeutic agent, but its biological half-life was too short. There was a rush to see what modifications can be made to GLP1 to make it last longer.

On the fork in the road: Coming back to me, it was clear at that time that if exendin 4 acts on GLP1 receptors it might be also be a therapeutic agent. I've worked in the VA my entire career; *however, the VA decided not to patent my invention*. In VA's defense, at that time VA was only interested in patenting inventions specific to veterans such as spinal cord injury, loss of limbs or prostheses. That would be very much VA/veteran related and they would have been interested in patenting that kind of invention. Now, VA has changed, so they are prepared to patent any

invention made in the VA. But back then it was different thinking in a different era. In fact, I would point to Rosalyn Yalow herself because Ros Yalow, along with Solomon Berson, invented radioimmunoassay. Ros herself said to us… many people thought radioimmunoassay should be patented. She refused. She said the work was done with government money; it's for the public good, and it should be in the public domain. However, radioimmunoassay did not need patent protection to be commercially developed. Exendin-4 required patent protection before any pharmaceutical company would risk hundreds of millions of dollars to develop it. In the memo, the VA general counsel said, "VA declines to patent," but went on to say, "You can patent it on your own." Here I faced a fork in the road and like Yogi Berra I took it.

On patenting and the long roller coaster ride: I'm a physician, a scientist, what do I know about patenting? On the other hand, unlike Rosalyn Yalow, if I thought, "If I don't patent it no one will touch it." Bringing a drug to market costs hundreds of millions of dollars. No pharmaceutical company would ever think about initiating drug development without patent protection. My conclusion was, "I have to patent it. Without a patent it has no chance of being developed." I found a patent lawyer in Chicago, and here I have to give my wife a lot of credit because the patenting process is like a roller coaster; a prolonged roller coaster ride. You don't know when it will end; you don't know what its prospects are for success. You apply for a patent, and it seems endless. Every month I received a bill from the patent law firm for expenses. My wife would say to me, "Why are you doing this?" I would say, "I have to." And then she would say, "Well, when is it going to end?" "I don't know." This went on month after month and she finally said, "Why are you doing this?" I couldn't think of a good answer so I said, "Well, it is my tuition." She was fairly tolerant. How long did it take? Two years. And not a smooth two years either. After a year it was rejected. The patent attorney explained that the Patent Office routinely rejected everything the first time around, basically placing the burden of proof on the inventor to clearly demonstrate that persons of ordinary skills could not have come up with the invention. After the first rejection, I sent rebuttals and responses to the Patent Office. Another year passed before the patent was finally awarded.

On calling all the pharmaceutical companies: How did I feel when the patent was issued? Both elation and dread because I now had to market it. What did I know about marketing? I remember calling up all the major pharmaceutical companies and most were not interested. For example, Merck's interest then was oral medications and not peptides, which have to be injected, like insulin. With other companies I talked to, exendin-4 represented something too risky. Large pharmaceutical companies face their own forks in the road. To commit to developing a drug is very expensive; phase 1 might be $15 or $30 million. Phase 2 is a whole lot more than that, maybe $50 to $100 million; phase 3 is tremendously expensive. They don't commit to initiating drug development lightly. On the other hand, if a biotech firm took the risk and developed it to a point where risk was much reduced then risk is more tolerable. I think large pharmaceutical companies are willing to pay more money for partially developed compounds with reduced risk. Actually, I got very good advice from a person who was working at Eli Lilly at that time. Richard DiMarchi was in New York visiting Mt. Sinai where I asked him about the prospects for exendin-4. He gave me very good advice and I still remember it clearly. I offered to drive him to the airport. On the way to the airport I said, "Look, I have this compound - would Lilly be interested in it?" He said, "The marketplace asks how is your compound any better than what's available?" Exendin-4 is a GLP1-like compound, so it had to be either more potent, or have fewer side effects or be longer acting than GLP-1 to have any value in the marketplace. I concluded that the competitive advantage, if exendin-4 had any, would have to be duration of activity.

On the excitement of testing diabetic mice: I set up an experiment with three groups of diabetic mice - one group was injected with saline or placebo, the other injected with GLP-1, and a third with exendin-4. Then I measured the glucoses in the three groups of mice over 24 hours. When I processed the data, the placebo group had high glucoses that remained very much elevated; it would be the equivalent of 300 mg/dl. In the GLP-1 group, the glucoses dropped dramatically to the mid-100s then started to rise at one hour, and by two to four hours it was back to their baseline elevated level. In the exendin-4 group, glucoses dropped dramatically at half an hour, stayed in the mid-100s and remained that way for hours. The animals varied, so some started to come back up within six or eight hours while a couple of animals had glucoses that remained in the mid-100s through to the next day.

On the VA: I can't speak highly enough about the VA. I'm been here my entire career - part of our mission in VA is research, and that's important. The VA's mission is to care for veterans, to train healthcare workers, to do research, and to serve as backup for the Department of Defense. It's estimated that 40% of all residents training in medicine have trained in the VA at some time in their career. The VA has a research career development program. I was part of that program; I entered the VA in the research career development program and spent nine years

progressing through it, which is a very large investment in individuals. As part of this program, my being a physician, they said, "The expectation is that you spend at least a quarter of your time in clinical activity." That's very understandable because if you don't engage in clinical activity you lose your skills are not exposed to clinical problems and needs. Three-quarters of the time I was in the lab doing experiments, the other quarter of the time I was seeing patients. I thought that was a good balance. And here I have to give credit to my wife for helping me to maintain balance in my life. The balance is: research, clinical activity, and family.

On the 1996 ADA meeting: I submitted an abstract to the annual ADA meeting on the experiment with diabetic mice comparing exendin-4 to GLP-1. It was accepted as a poster presentation at the ADA in the summer of 1996 in San Francisco. Andrew Young of Amylin came by. Richard DiMarchi at Lilly was also there. He invited me to give a talk at Lilly, which I did. It was a very interesting experience. Pharmaceutical companies have personalities. At Lilly, I was scheduled for meetings every half-hour for the entire day. I talked to everyone including people in chemistry, manufacturing, and physiology. I remember it was like a job interview. They wanted to fully understand exendin-4 and reduce their risk to the greatest degree possible – it was if they were looking for things that could go wrong. At the end of the day, I still recall, the final person I saw was Jose Caro. He said, "Thank you for coming." I asked him, "Well, is there an interest?" And basically he said—I don't really recall what he said—but basically he said no. Depressing. Exendin-4 didn't clear the hurdle. But Andrew invited me to Amylin. They moved quickly – I gave a talk, they said they were still interested, and we negotiated a license. That was October 1st, 1996. I have to say this, one of the really wonderful things about the United States are biotechs willing to take risks that larger companies may not be willing to take and run with it. I don't think the risk-taking culture exists in Europe so much; it's one of those things that make the United States so great. The willingness to take large risks, and, of course, to have the rewards that come with success.

On the post-licensing trajectory: My trajectory after the licensing was this: as part the research process in academia we make research proposals. The proposals are evaluated, and either you get funded or you don't. I had submitted a proposal that came back with the comment that this proposal has merit, but it is most appropriately done by a pharmaceutical company. I read it and thought, yes, that's right. That really was correct. So I said at that point I'll stop research and move on to a different career, which I'm still in, bringing electronic medical records into use to replace paper records. In 1996 the VA system rolled out an electronic medical record; and I became the manager. An entirely electronic medical record feeds into a database that in turn supports a better kind of healthcare delivery. For example, at the Bronx VA we have 25,000 active veterans. Querying the database shows there are 4800 diabetic patients. This group can be characterized in great clinical detail; what medications they are taking, etc. To me, electronic records have powerful potential for improving health care. For example, during the flu season, we can define risk groups and then track what percentage in each risk group had flu vaccine. One of the risk groups is transplant patients, 50 with transplants of any kind, five with heart transplants, four done at Columbia Presbyterian and one at Mt. Sinai. We still ask the same question: how many of the transplant patients had their flu vaccine? It's a very powerful – this is where health care is headed in the near future. The VA has a program for improving health care by comparing itself to measurable benchmarks with other healthcare systems. Among diabetics, how many have had a hemoglobin A1c? How many diabetics have had their annual retinal exam; how many have had their feet checked for loss of sensation. These are all public or health care benchmarks where the VA can say, "This is how we compare to other health care systems." And I'm part of VA's movement to measure and establish quality markers in clinical care. I think it's just great for health care, not only for individual patients, but for groups of patients – it helps ensure uniformity in health care. The aim is to assure that all patients receive equally good health care. We look at everyone in this system to determine which healthcare services each individual should be receiving. You could call it my second career in the VA, as Director of Clinical Informatics here.

On stopping research: I thought exendin-4 was in good hands at Amylin. I wasn't interested in starting a completely new direction in research, so I reinvented myself in another emerging field, clinical informatics. I think it turned out right; if exendin-4 were a child, at a certain point of the child's development you have to say, "I trust the teachers will take care of this child's further development." That's the way I saw it.

On challenges of research: To me the hard part is finding something new. There are no guarantees to discovery. You explore, you take a certain path and follow up whatever that path brings. In terms of obstacles, the hardest part was doing many things well. To my endocrine fellows, I ask, "Can you do one thing well?" And they say, "Yes, yes we can do that." And then I ask them, "Do you think you can do two things well?" And they say, "Yes, it's a little harder, but we can do two things well." "What about doing three things well?" Meaning research, clinical practice,

and family—my life revolves around those areas and I suspect theirs will too. Doing three things well… doing three things *well* is very difficult. That's where you have to make choices; without a supportive family, it is nearly impossible. I am a strong believer in having a balanced life. It's a blessing to have an interesting life but sometimes very difficult!

On Exenatide's clinical path: It's really thrilling to follow Exenatide's development. I'm an outsider because I'm not engaged in its development, but it's wonderful to see. Again, I see its development like that of a child. As your child develops you have great pride in the child. You send it off to higher levels of school where the child develops in larger environments. In my case, the child and the development were guided flawlessly.

On watching development: Again, like any good parent, I have my fingers crossed and hope nothing bad happens. It really is like that. It's not only the good things but also the absence of bad things. Maybe I'm taking the child analogy too far but we have hopes for children; we have hope that the child will not only do well but help mankind in some way. I know my parents had the same hopes for me; that I would do well and contribute to mankind in some way. This is so satisfying.

On whether he will go to ADA this year: I have to choose. I usually go to the Endocrine Society for continuing medical education credits. *(Ed. Note – at this point, we tried to convince John he should attend ADA this year to see Byetta launched!)*

On hypoglycemia: One of the more important problems that we face as clinicians is hypoglycemia. Exenatide is potentially one of the therapies that will reduce the incidence of hypoglycemia. From a clinician's point of view that's an important problem and Exenatide a good solution. I had a patient on insulin trying to achieve tight control who was having hypoglycemic events. I said to him, "Look, you have to cut back. You can't afford to have such frequent hypoglycemic events." He said, "No, I can't." I asked him why? It's not good for you. He said, "My mother had diabetes, she had two of her legs amputated and I don't want it to happen to me." Then a month later I learn he was hospitalized because he crashed his car; fractured his pelvis probably because of hypoglycemia. If it could prevent some of these things from happening it would be wonderful.

On the competitive landscape: I'm a biased party. I am biased for Exenatide, and I hope it does better than competing agents. However, I also see things from a patient's point of view. With that in mind, really, what is best for the patient is, in the end, what counts. It won't be a single compound. It will be multiple compounds. With Exenatide, it's like software - there's a version 1, a version 2—so there will be evolution there too. LAR? Oh, I can't talk about that…

On education: A major portion of my time is spent educating patients. Patients make decisions about their care. To educate the patients I tell them that the better the diabetes control the less the chances of complications occurring. The goal is to prevent or delay the complications of diabetes. Education is always difficult, however, which is why the simple therapies that work are wonders.

On how more partnerships could be made: The United States has been an incredible engine for innovation and bringing new products to markets, essentially, transforming health care into something we could not have envisioned 10 years ago. How to do it even *better* requires innovation on the part of big pharmas, small pharmas, and biotech. Making a discovery is the first step, but then how do you translate--move that discovery from bench to bedside? There ought to be many models, not just one. If one doesn't work there should be an ability to look to another model and yet another model after that. This is what we need to work on.

Editor's final note – there was a slight lag with the interview and our final question – we were in touch with John briefly on Saturday, April 30 with one final question for him.

On how John learned about the FDA approval of Byetta. [Amylin Chief Operating Officer] Dan Bradbury called me with news of FDA approval on Thursday April 28 at 9:30pm Eastern. I did not have much sleep the rest of the night from the excitement. My hope is Byetta will come to mean excellent diabetes control. That would be music to my ears.

-- By Martha I. Nelson and Kelly L. Close

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