

DIABETES CLOSE UP

Diabetes Close Up
January 2006, No. 55
Diabetes Hits the Mainstream

The Shorter Version

From the Editor:

Diabetes is really in the headlines. First, it's top of mind because of inhaled insulin – Exubera just received its long-anticipated FDA approval today (January 27) and EU approval yesterday (January 26) – and, as such, is gathering a lot of coverage. If it's priced reasonably, which we'd peg at \$3-4/day, and reimbursed well (a question that can't truly be answered for months), we believe insulin use will become more prevalent in the late-in-disease-progression type 2 patients, many of whom are simply ignoring their need for it now. Inside are details on the approval, post-marketing surveillance studies, and implications for the diabetes industry.

Second, diabetes is all over the media. You undoubtedly saw, for example, the recent New York Times four-day, 24,000-word series on the ravages of type 2; if you didn't, we urge you to spend some time with it at www.nytimes.com/diabetes. Three top reporters spent a year focused solely on diabetes; clearly, the disease is gaining traction as public health crisis. We believe the series could have a wide-ranging impact in public policy at all levels of government, and we hope in particular that it can begin to improve reimbursement, as we are becoming increasingly nervous about the departure of diabetes healthcare providers and the dearth of candidates entering in the field. Inside is our take on the series, informed by some fascinating conversations with the series' authors.

Third, we saw more recognition of diabetes at an obesity Town Hall meeting on Saturday, January 21 in Memphis. We were fascinated to attend this community function, as we believe that stemming the tide of obesity will have to start at the local level. Just before that, we attended an American Heart Association conference, "Obesity, Lifestyle, and Cardiovascular Disease" – doesn't that sound foreboding! It should.

This month also saw greater scrutiny on inpatients and insulin intensification. We attended one conference, the Society of Critical Care Medicine's annual meeting, which lies under the radar screen for the diabetes community, but it offered tremendous insights on the shortcomings of diabetes care in hospitals, which we share with you later in this report. Now we're preparing with huge excitement for an AACE and ADA-sponsored meeting that starts January 30, "Improving Inpatient Diabetes Care: A Call to Action Conference," which is well above the radar screen. As we wrote on our blog on January 3, this meeting is absolutely a "can't miss" – indeed, it's sold out, but we'll be reporting on highlights next week from DC on our blog and in the next DCU.

Last, on the more general theme of glee, January is one of our favorite months. It begins with the annual JP Morgan conference, which takes place in Close Concerns' hometown, lovely San Francisco. This year's stellar conference (really, what would any healthcare investor do without it? It has become such a welcome and productive way for everyone to start the year) reminded us of how pervasive diabetes businesses and programs are becoming – following this has been terrific fun! Earnings season itself has

now begun and as we type, we're in the midst of it – see page 9 for 18 company updates, which we'll continue next month.

Finally, thanks to the dozens of you who filled out our online survey for this newsletter. If you haven't filled it out and would be willing to, we would love it as we're learning so much that we hope to incorporate over the coming months. Please go to www.closeconcerns.com and click on "reader survey" to participate or click directly on <http://www.surveymonkey.com/s.asp?u=348361538634>.

--by Kelly L. Close

In this issue:

1. Exubera approved! – page 5

**2. *New York Times*'s series puts diabetes to the fore as an urgent epidemic – page 6
DCU interviews NYT reporters behind sweeping 'Bad Blood' series on diabetes – page 9**

3. DCU Company Watch - page 10

- **Sanofi – Big questions abound**
- **Novo 4Q05 – Analogs are booming and what's the subpoena all about?**
- **Lilly 4Q05 and at JPM – Highlights Byetta, LAR, retinopathy**
- **Amylin at JPM – Firing on all – *all!* - cylinders**
- **Becton Dickinson F1Q06 and JPM - Diabetes products as 'major revenue drivers' – thanks, Amylin!**
- **BMS 4Q05 – Saxagliptin benefits from 14% 4Q R&D spending increase**
- **Abbott 4Q05 – Overachieves on \$1.0 billion sales milestone**
- **J&J 4Q05 – Achieving \$1.9 billion in LifeScan sales and looking forward to continuous**
- **Pfizer 4Q05 – Ready to inhale**
- **Novartis 4Q05 – Preparing the DPP-IV**
- **GSK – OTC panel comes in as expected**
- **Insulet at JPM – First corporate presentation draws SRO crowd**
- **Medtronic at JPM – Prepares for broad launch of sensor-augmented pump**
- **Merck at JPM – Tight-lipped on diabetes**
- **Alkermes at JPM – "A freight train of forward inertia,"**
- **Arena at JPM – Grooving on work in diabetes and obesity but no real news**
- **Biovail at JPM – Combo drug to combat compliance issues?**
- **Emisphere at JPM – Generating phase 2 data for oral insulin**

4. Scrutiny on diabetic care in hospitals raises hopes for improved treatment – page 18

5. Improving Inpatient Diabetes Care preview, Washington DC, January 29-31 – page 20

6. Focus on Obesity: from the AHA obesity conference to a Memphis town hall meeting – page 20

7. Literature Review: *Nature Genetics*, Scientists discover gene for type 2 – page 22

8. Literature Review: JAMA reports that being overweight increases risk for CHD independently – page 24

9. Literature Review: NAVIGATOR data yield link between nonalcoholic fatty liver disease and CVD risk in type 2 patients – page 24

10. Conference Review: Dr. Steve Edelman's "Taking Care of Your Diabetes" – page 25

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.

- 1. January 27: This month's *Diabetes*: Nitric oxide as a potential new treatment**
- 2. January 26: NYT profiles stem cell researcher Doug Melton**
- 3. January 26: Abbott Diabetes Care exceeds \$1B in revenue**
- 4. January 26: BMS 4Q05 results – Saxagliptin benefits from R&D increase**
- 5. January 26: Exubera earns EU approval – look for U.S. approval any minute!**
- 6. January 26: Amylin still on fire - 4q positive preannouncements**
- 7. January 26: Novartis 4Q05 results – How to not say very much**
- 8. January 25: Obesity now a French concern – *what?!***
- 9. January 25: JNJ reports whopping \$1.9 billion in sales for 2005**
- 10. January 20: AHA obesity conference – commentary on obesity drugs**
- 11. January 13: Pfizer takes back inhaled from Sanofi**
- 12. January 13: Final segment of NYT series focuses on diabetes in Asian populations**
- 13. January 12: Lilly at JPM – full steam ahead!**
- 14. January 11: Third day of NYT series gets it exactly right**
- 15. January 10: Merck - ... And?**
- 16. January 10: Day 2 of NYT: ' Living at an Epicenter of Diabetes, Defiance and Despair'**
- 17. January 9: Amylin on fire**
- 18. January 9: Sobering in-depth NYT piece highlights ravages of type 2 epidemic**
- 19. January 6: Guardian RT blog bodes well for continuous**
- 20. January 5: Getting a diabetic pancreas to regrow its islets**
- 21. January 3: BW on Amylin – Excellent PR for 2006**
- 22. January 3: JPM meeting starts this week!**
- 23. January 3: Hospital meetings abound – AACE/ADA Inpatient “can’t miss” meeting**

The Longer Version

1. Exubera approved!

Pfizer announced today (January 27) that its first-in-class inhaled insulin, Exubera, has received FDA approval, following the September 8 panel's 7-2 vote to approve it for adults with type 1 and type 2 diabetes. The decision was expected today, as the FDA had declared a 90-day delay in decision on October 27. Pfizer hopes to have Exubera available by mid-year, a bit later than might otherwise be expected, though we suspect the slightly longer timeframe will enable the company to make sure all the support is in place prior to launch to ensure an ideal market introduction.

While Pfizer and Nektar are the immediate beneficiaries, Exubera's approval also bodes well for other companies developing inhaled insulin, including Lilly/Alkermes, Novo Nordisk, Mannkind, and Kos Pharmaceuticals. The approval may also augur well for companies pursuing alternate delivery programs (e.g., oral, transdermal, etc.) although such approaches appear to suffer from significant technical hurdles that Pfizer's success won't help. Ironically, while the approval may assist Lilly and Novo because they have earlier-stage programs that may now move faster through the FDA, and more importantly, the reimbursement hurdle may be smaller by the time of their submissions, those very companies, as well as Sanofi, now face a formidable new insulin competitor in Pfizer. Ultimately, we think Pfizer will do more to *increase* the size of the estimated \$7+ billion insulin market than anything, but certainly short term, Pfizer will steal some market share from the entrenched players. That isn't good news for Lilly and Sanofi-Aventis, who are also facing new pressure from Amylin, whose product Byetta is keeping other patients from moving to insulin.

As expected, Exubera has been contraindicated in patients with chronic lung disease, including asthma, chronic obstructive pulmonary disease, and emphysema. It is also contraindicated in patients who smoke or who have smoked in the six months¹ prior to initiating inhaled insulin therapy. Obviously, safety is obviously a critical issue. Exubera's long-term effect on lungs, for example, will remain unknown until the drug has been widely used in large populations for an extended period of time. Certainly on some level, the approval would seem to indicate that the FDA has confidence in Exubera's safety. When we learned following the panel meeting that the negative votes were from pulmonary specialists, this did give us pause. We would expect now that the drug is approved, however, that it'll be all up to Pfizer to do all in its power to make sure it is used in the right populations – certainly in the wake of safety disasters in recent years (e.g., Vioxx and Rezulin), the appropriate incentives (or reverse incentives) do seem in place.

Additional safety concerns with inhaled insulin center on antibody formation and pulmonary function. On that note, the label for Exubera recommends lung function testing at the start of treatment, as well as at six months, at 12 months, and annually thereafter.² Importantly, we understand that Pfizer has committed to significant long-term safety studies, including a large, five-year study, a seven-year epidemiological study of chronic lung disease, a three-year phase 4 pediatric study, as well as additional other mechanistic studies.

¹ We think that this is on the lower side of what could have been the length of time after patients quit smoking before which they can begin inhaled insulin – for a smoker, the absorption of inhaled insulin is much greater (50% more in some studies) and is unpredictable, with greater intrasubject variability. The peak concentration of insulin is earlier and greater in smokers, meaning that the risk of hypoglycemia jumps. So, what if patients *lie* about whether or not they smoke? Not great. This is a very big deal for any type 1 - for type 2s, it's still a risk, but type 2s are more protected from severe hypos with insulin resistance.

² Although the FDA press release stated that lung function testing was recommended to be repeated "every 6 to 12 months," Pfizer management told us that this was an error in the FDA release.

Pfizer/Nektar have achieved broad indications, with Exubera indicated for type 2s both as a monotherapy and in conjunction with longer-acting insulin or oral agents. It has also received approval for type 1s in combination with long-acting insulin. Exubera is *not* approved for children, and it is not clear if full data from the pediatric study will be needed to support a pediatric submission. We see the broad label for type 2s—with Exubera as *either* an add-on or a monotherapy—as an important distinction that creates an open market for Pfizer.

Two major questions remain - pricing and reimbursement. Success will require reasonable pricing, reimbursement from CMS, and top-rate education for healthcare professionals and patients. On pricing, we see \$3-\$4/day as reasonable, but apparently specifics on pricing won't be available until launch.

What about demand? Dr. Bernie Zinman, a renowned diabetes specialist, said uptake “*will absolutely be driven by patients*” and we believe their enthusiasm will be driven by reimbursement. This approval is, Zinman said, the “holy grail” for some groups of patients who have heretofore refused to take insulin even though they were not at goal – as a reminder, about two thirds of patients in the US don't achieve the ADA recommended A1C of 7.0.

Clinicians appear to be cautiously optimistic. Dr. Jay Skyler, Professor, Division of Endocrinology, Diabetes, & Metabolism at the University of Miami, who has been using inhaled insulin in clinical trials for ten years, noted that it has its limitations: “You can get more precision and glucose control with pens than with this, because you can titrate a little better.” But, he added, “This will improve glycemic control in the population at large. Not enough people take insulin of those who need to take insulin – this will facilitate people going on insulin earlier. The overall A1C of the population is going to end up getting better.” In our view, given the poor outcomes, and given that outcomes have continued to worsen over the last decade, that's the be-all, end all – the positive public health implications of people with the *worst* outcomes taking insulin after years of refusing could be immense.

Ultimately, we see the availability of inhaled insulin as a significant positive in that it generates another option for patients and will hopefully accelerate, or at least facilitate, a nationwide move toward tighter control. Safety must be watched extremely closely, and we are pleased that Pfizer appears to be mindful of this – undoubtedly, bad things could happen that didn't arise in the 2,500 adults in whom Exubera was tested.

In terms of patient use, we are watching closely to see how the market will break down between injectable insulin, Byetta, and inhaled insulin, as a type 2 patient not at goal will now have a choice among the three. Dr. Zinman told us that he believes the options will hasten the transition to additional therapy that patients often resist: “*This will capture the imagination. Patients know when they need to be on insulin, but they aren't prepared to take the step. Now I can say to them, ‘You have options. You can take a single injection of Lantus. You can take a twice-daily injection of Byetta and you may lose weight – at which their eyes may brighten up. You can take an inhalation of medication at each meal. I'm not sure which way patients will go.’*” We will be watching.

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

2. *New York Times's* series puts diabetes to the fore as an urgent epidemic

The New York Times's ambitious four-day series on diabetes, beginning on January 9, was unusual for its length – about 24,000 words, plus color photographs, charts, graphics, and webcast interviews with the reporters who spent more than a year on the project. Significant wars have received less attention. It's safe to assume the *Times* will nominate the series for many awards, including the Pulitzer – while it's only January, we certainly feel it's worthy. While we have some concerns about the articles, namely in the possible misperception that diabetes is mainly a lifestyle disease, we salute the *Times* for thrusting

diabetes into the fore as the most urgent epidemic of our time. We also commend the newspaper for highlighting the inadequacies of our twisted reimbursement system, which effectively rewards poor care and contributes to bad outcomes of many chronic diseases.

The series's title, "Bad Blood: The Stealth Epidemic," conveys its view of diabetes as a grim, insidious condition, hampered by a Third World healthcare system, helpless against a cultural tide of obesity, virtually without remedy. The most obvious question raised is whether this increased attention will lead to more funding for research or for improved care. No one knows, but at least government leaders, public health officials, and insurance executives can no longer plead ignorance about the syndrome's awful toll. Indeed, the series underscores that the US health insurance system is geared to pay for major reactive work such as surgery, procedures, and some drugs, but not for proactive disease management like training, counseling, fitness, and diet education. Doctors, nurses, and hospitals receive no incentive to keep patients healthy. To boot, mainstream agribusiness, junk food outlets, the media, and ubiquitous processed food companies combine to deter healthy eating habits. Finally, of course, few are exercising sufficiently, with little reason to interrupt their demanding work or TIVO or social schedules. This isn't everyone – but how many patients are at goal?³

It is time to step off our soapbox for a moment to offer a brief recap of the series, though all the stories can be accessed at (www.nytimes.com/diabetes). The articles focus on type 2 diabetes exclusively, specifically its impact on low-income minorities in New York City. The first story provides an overview – the number of people affected (21 million total; 800,000 adults in New York); the disproportionate impact on minorities (blacks and Hispanics develop it at almost twice the rate as whites); the impending crisis (41 million pre-diabetics in America; one in three born now expected to get it); the financial cost (the \$132 billion a year quoted is a low estimate in our view) and physical fall out (amputations, blindness, kidney failure, and all flavors of cardiovascular disease).

The second story examines East Harlem as a diabetic epicenter, where 90% of the community is Hispanic or black, over 30% are obese, and 16% have diabetes. By contrast, the community immediately south, the Upper East Side, is richer, whiter, and thinner - just 7% obese - and has only 1% with diabetes. East Harlem's diabetics lack adequate health care while suffering from an abundance of junk food, video games, and just plain indifference. Diabetes causes 10 times as many hospitalizations here and five times as many deaths.

The third story describes the demise of three diabetes centers in New York, all victims of a healthcare system that generously funds treatment of acute illnesses while shortchanging care for chronic disease. Insurers, for example, balk at paying \$150 to a podiatrist who can detect a foot ailment, while not blinking at a \$30,000 bill to amputate the same foot. We found this piece the most troubling, for it vividly highlighted what was for us the biggest truth of the series— *prevention of diabetes doesn't pay*. What's more, complications of diabetes do pay. In light of this mess, it shouldn't be surprising that endocrinology is virtually the lowest-paid medical specialty and that we'll have another different crisis on our hands in a decade or two when there are no specialists left to treat the most complicated cases or to train general practitioners. Veteran *Times* reporter N.R. "Sonny" Kleinfeld, the author of the first two articles in the series, commented in a recent conversation with us: "Compared to some other medical specialties, endocrinology is a low-paid, underappreciated field. This seems illogical at a time when diabetes is expanding at such a relentless pace." We concur. Walk around the ADA in Washington this June and see how many endocrinologists there are under 40. Very few. The doctors and CDEs in the field deserve medals, given their paltry reimbursement fees. But go to the orthopedic surgery meeting or the bariatric

³ About a third, according to the literature, but this is overstated in our view because: 1) We suspect patients who aren't doing well aren't being followed; 2) the association goals are going to go down any second – or at least, we imagine, by the time ACCORD results come out.

surgery meeting or the cardiac surgery meeting – they are teeming with young doctors. We don't object to paying knife-wielding surgeons for acute problems, but the US needs to increase reimbursement to providers who use cognitive skills in treating chronic illnesses.

The last story was actually two stapled together as one: the first looked at how new immigrants from Far Eastern nations like China, Korea, and Japan suddenly found themselves overweight from our junk food diet and highly vulnerable to diabetes, a trend that could soon make New York “a colony of the sick.” The second showed how these unhealthy trends have been abetted by snack food and candy companies that blitz children with ads and by a government that grants tax breaks to fast food restaurants, cuts funds for physical education classes, and rejects proposed legislation that would force restaurants to post nutritional information on their menus.

Given the scope of the problem, no series can be truly comprehensive. One quibble with the *Times*' effort is that it may have misled readers who are just learning about diabetes. While it's entirely appropriate to highlight its disproportionate impact on minorities, the *Times* ultimately published a narrow patient profile – it's a truer profile than for New York than elsewhere and granted this was a Metro series after all – but this group isn't an exact copy of the group at risk in the US. According to the CDC, at least 20 percent of type 2 patients are *not* obese, many are white, and the other factors contributing to obesity – genetic and biological, the entire “thrifty gene” theory of evolution – are all but ignored. To read the *Times*, you might think that diabetes is a self-imposed disorder among indifferent, overweight minorities.

And, of course, there is virtually no mention of type 1 diabetes, other than that it exists, though type 1 is also increasing, at least in certain sub-groups such as under age five, for reasons that researchers don't understand.

Ian Urbina, one of the reporters on the series, said they tried not to make false generalizations. “We wanted to be very sure that we weren't isolating unusual phenomenon but that we were highlighting common, undiscussed phenomenon,” he told us in an interview.

Our concern is that the *Times* series could harden perceptions that diabetes is principally a lifestyle-driven disease, which can be remedied by personal will power and discipline. Is your blood sugar high? Lose thirty pounds and stop eating Twizzler sticks. Such a view, of course, is simplistic if not outright wrong, but it could hamper efforts to raise research money, public or private, on the grounds that there are more “deserving” causes or to limit reimbursement reform. This obviously was not the reporters' intent, but it could be an outcome.

A more optimistic view is that the series will serve as a call to action for more funding for preventative care and for research on complications. We hope that is true, but given the recent cuts in the NIH's budget for medical research – the NIH projects a decline in the number of research grants for the second consecutive year in 2006 – we aren't holding our breath.

Several readers asked us what we thought the *Times* omitted from the series. Well, the first thing most people want to know about a horrific disease is – will there be a cure? If so, when? If not, why not? The *Times* ignores these questions completely, though not without reason. Urbina said the prospects for a cure “are not far enough along” to draw much attention. We fear that's true. At least researchers know that type 1 involves an autoimmune trigger, but they know even less about type 2, in which the body becomes insensitive to insulin or produces insufficient amounts. The *Times* also provided little coverage about new therapies or drugs that may hold promise for patients. This too is revealing. It is hard enough for patients in East Harlem to buy fresh vegetables and viable glucose strips. New therapies, even if they work, are typically expensive, and they are more likely to be used by more affluent, fully insured patients.

If nothing else, we hope the series forces payers and providers alike to realize that more money needs to be invested in preventative care, as well as training and education, so patients have the necessary tools to care for themselves. If it does this, that would be a major achievement. If not, today's bleak landscape, in which the disease seems beyond the reach of the healthcare system, will take root permanently, and the doomsday scenario conjured by the *Times*, in which Americans in the future are obese, crippled, partially blind, desperate, despairing, and diabetic, may come to pass.

—by James S. Hirsch and Kelly L. Close

***Times* Reporters Discover Grim, Overwhelming Story**

The *Times* series was classic journalistic approach of homing in on one problem – diabetes – as a microcosm of a much larger issue. "The story was attractive because diabetes seemed like a good test case of how the entire health care system handles all chronic conditions, which in a lot of ways are probably going to be the most difficult to handle in the next several decades," *Times* reporter Ian Urbina told us in an interview. "Diabetes seemed like a good stand-in for all of those conditions as we move forward."

The idea for the project came from an editor who had previously written about asthma and was interested in chronic diseases. Urbina said the reporters wanted the story firmly located in New York, and the demographic data for East Harlem caused that community "to jump off the page." Prevalence of diabetes was high, combined with a working class neighborhood, poverty, fast food restaurants, and the lack of fresh foods. "All of those things conspired in a perfect storm in that neighborhood," Urbina said. "It was difficult, in fact, to walk through East Harlem and not find someone who wasn't related to someone with diabetes."

The series's tagline, "the stealth epidemic," reflected not only the lack of attention that diabetes has received from society at large but also from individual patients. As *Times* reporter N.R. "Sonny" Kleinfeld told us, "Even in families hardest hit for years and years, knowledge is feeble. People, even patients, so underestimate the disease. We kept hearing, 'I never thought it was that bad.' Diabetes doesn't hit even the top-ten list in terms of most patients' realities or priorities."

The reporters had to invest considerable time with patients before they would talk candidly about their condition. "People are reluctant to talk about their own struggles with their own body, so you really have to cultivate relationships with them to get a level of specificity," Urbina said.

What emerged in these conversations was a deeper appreciation of the true scope of the problem. "The psychological contours of this disease are truly enormous," Kleinfeld said. "Society has totally failed these patients."

As grim as current conditions are, the reporters concluded that the future looks even bleaker. Consider the shrinking number of diabetes care providers. Urbina said the shortage of endocrinologists and diabetes educators – in New York, there are about 100 for 800,000 patients – precludes effective care. "Those who are providing care are outgunned," he said. At the same time, doctors told Urbina that less than 5% of their medical school education was devoted to chronic diseases. "When they got out, they realized that it was the diseases that they'd studied so little of that were actually prevalent in society," he said.

What makes the disease difficult to solve, Urbina realized, is it that requires major changes in both the healthcare system as well as changes in individual behavior. How big is the challenge? So big, that even a monumental four-part series wasn't adequate. "To be frank," Urbina said, "it was difficult to cover all the bases even in the amount of space that we had."

—by James S. Hirsch and Kelly L. Close

3. DCU Company Watch. *WOW so much news this month! Our first piece below is on Sanofi – some big picture thinking. The next eight pieces focus on companies that have reported results in the last couple of weeks or have had big news otherwise – we point out J&J and Abbott as ones to read to get a sense on where blood glucose monitoring (and diabetes management) is headed and on Lilly, BMS, and Amylin to get a sense on where things stand on the new drug front. The last nine pieces focus on companies that presented at JP Morgan’s outstanding conference here in San Francisco earlier this month – there, we saw Insulet representing by far the high point of the meeting in terms of “new” news.*

SANOFI – Big questions abound with Acomplia: So what happens with Acomplia? The cheers have begun, and some might think this addiction drug is already on the market! We think eventually that this drug will be big, complementing a number of diabetes therapies (Byetta, insulin), *but* the CNS issues that have surfaced in trials aren’t trivial and shouldn’t be treated as such. So what could happen? Outright approval (for some as yet undisclosed indication, perhaps lipids – as a reminder, we don’t even know for what indications it has filed), a process sort of delay (like Exubera’s delay before approval), an approvable letter accompanied by a request for more data, an approvable letter that is a little less scary, or no approval.

- We doubt we’d see outright approval with no panel meeting, and if there were going to be a panel meeting we would know.
- Delay – hmmm, maybe.
- Approvable letter – this is where our vote is. The FDA gets some credit for moving this obesity compound forward, but it doesn’t have to make this drug available with insufficient CNS info. What the letter will demand is the question of the day!
- No approval – we won’t see this because we don’t believe the FDA wants to be associated with any drug that could potentially help control obesity.

NOVO 4Q05 – Analogs are booming and what’s the subpoena all about? Novo certainly had a superb finish to the year, reporting earnings on January 27. It now supplies 51% of the insulin sold globally and 34% of the analogs, up from 50% and 28% a year ago – clearly, Novo is both winning new patients over and expanding market share. In the US, the total and analog insulin market shares are 38% and 23%, respectively, up from 34% and 18% a year ago - they are on a serious roll in the US as well on the analog front! Total diabetes care sales were 33.8 billion in Danish kroner (\$3.9 billion). Insulin analogs grew to \$1.2 billion, up 61%; human insulin and insulin related products grew to \$2.4 billion, up 3%, and oral agents (Prandin) was nearly \$300 million, up 3%. Worldwide sales of Prandin came in at \$280 million, up 4%, though Prandin sales fell in the US. To bolster the growth, and in preparation of the Levemir launch, which will take place second quarter, Novo now has 1200 on the diabetes care sales force.

On the R&D front, Novo has filed for approval of Levemir in Japan - if it gains approval, it would be the first and only company, as in the US, to have rapid acting, premixed and long-acting insulin analogs. In Japan, a filing for NovoMix 50 got sent back from regulatory authorities. They should be able to get this approved there, but they have to do more trials. They didn't say much about liraglutide, except that phase 3 trials (n=a whopping 3,800) are still expected to start next month. On the inhaled insulin front, Novo took time off to do some strip and device optimization and validation - they should be able to go back into phase 3 this quarter. There are three early-stage drugs listed on the pipeline - two insulin analogs, including NN9101, a glucokinase activator, another insulin analog with some smart properties they won't disclose and one oral drug - they are all in phase 1. In response to how long phase 3 would take for Liraglutide, management said that there are no technical bottlenecks, and FDA submission in 2008 is still the plan. In the meantime, we may see some smaller deals, as management said it had been discussing in-licensing and acquisitions.

Oh no! The end of the press release notes that Novo got a subpoena calling for them to give all documents

relating to US marketing and promotional practices - the release says Novo "believes" this is limited to its insulin products and is "cooperating with the US Attorney in this investigation." Is an industry crackdown in the works? It's too early to speculate, but our attention is piqued.

LILLY 4Q05 and at JPM – Highlights Byetta, LAR, retinopathy: Lilly announced results January 26. \$49 million in 4Q Byetta revenue (which was pre-announced by Amylin an hour before the call) was the highlight of the call in diabetes news. The submission of Byetta in Europe was a highlight of the quarter, although it had been announced at the company's December analyst meeting. Lilly's Diabetes Care revenue rose 11% to \$750 million for 4Q, from \$673 million a year ago. US sales of diabetes care products increased 17% in the US and 5% internationally - that reflects the greater weight of Humulin (basically a pretty old insulin) outside the US. In our view, the company is going to continue to struggle without a long-acting analog and with an "older" rapid-acting analog. Humalog is getting pummeled by Novo's Novolog and has more competition coming through Sanofi's Apidra. Without the Byetta revenue (Lilly got \$26 million), Lilly's diabetes care franchise would've risen only 7.5%. "Newer" products contributed to 20% of total sales, compared to 14% a year ago. For 2005, diabetes care sales reached \$2.8 billion, up 7%. DPNP (diabetic peripheral neuropathic pain) accounts for 15% of Cymbalta revenue. Lilly characterized diabetes, obesity, insomnia, and Alzheimer's as four disease areas it is particularly focused on due to high needs.

Q&A on the conference call had few diabetes questions, except one, which asked about the acceleration in Lilly's insulin business as another 2006 goal and how the company felt on the eve of potential approval of pulmonary insulin. The company said it was very enthusiastic about inhaled insulin and thought Lilly's inhaled would be very successful, though Lilly is about three years behind, in our estimation. Executives cautioned that there were a lot of unknowns, such as pricing and uptake and overall, how things would go with the launch.

On the pipeline chart, Arxxant is still noted as an end of 2005 submission, though this was delayed in December. At JPM, Lilly showed retinopathy (40% relative risk reduction in sustained moderate vision loss) data as well as information on a nephropathy pilot, suggesting that that indication is back *ON* again. We loved the firm conviction we heard at the JPM presentation that diabetes would be the future of the company again – at least a very big catalyst. We think Lilly must be extremely excited about LAR, Amylin's follow on product for Byetta Classic – as a reminder, LAR is a once-weekly injection. We realize it knows more than anyone else about LAR (save Amylin itself), so we find the conviction real, as in multiple billions. As always, one must always follow LAR enthusiasm by noting the small data set.

Key to keep in mind is that in addition to the weak performance of Humalog, Actos (the TZD it helps market) will be gone soon as its agreement with Takeda ends at the end of 2006. On the other hand, Byetta is just getting started, and we look to see Arxxant emerge sometime soon, which would be an upside by anyone's definition. On drug development more generally, management discussed using more biomarkers and making decisions earlier in the clinical work, with more phase 1 go/no go decisions.

AMYLIN– Firing on all cylinders: Amylin is on fire. First, exactly an hour before Lilly reported on January 26, the company pre-announced \$49 million in sales for Byetta for the fourth quarter, well above expectations of ~\$33 million. Second, CEO Ginger Graham gave an outstanding talk at JPM; while we suspect the company would never take a victory lap because it's so busy running its business, if ever a company deserved it ... Amylin had two novel drugs approved last year, launched both drugs successfully, has two other drugs extremely close to phase 3, and has two new novel compounds hitting the clinic this year, and already roundly beat expectations for Byetta for the first year on the market – possibly Symlin too, though we won't find that out until the company reports February 9.

We continue to think Byetta/LAR's long-term revenue estimates are low and that Symlin medium- and long-term revenue estimates are lowish. In our view, it's all only going to get better. Many eyes are on

daily and weekly script watch. We're confident that more than enough patients are going on and staying on Byetta and Symlin, and we just hope that the HCP training can happen quickly.

Of note, another clinical trial begins shortly for Amylin, a randomized, open label trial. The number of patients is unknown, as is length of time, but we'll be following this closely. Terrific data of course came out in mid-2005 on LAR - probably the best data, full stop, that's really ever been seen for a phase 2 trial. Small number of patients, yes, but truly remarkable, all of it – the A1C drop, weight loss, tolerability – so it will be wonderful to see the results of another trial.

Some excellent details during the JPM talk were on Amylin's market research in late 2005. We have known that Amylin's medical education is top-rate, but we suspect the education got even better after launch, when the docs could talk about real-life use, not just trial data. That said, we were duly impressed by talks at AACE, ADA, AADE, and EASD. Interestingly, at JPM, we learned that 70% of Symlin users are type 1; the penetration potential left here in type 1 patients as well as the upside in type 2 is significant, in our view, especially as type 2 patients take two to four times as much Symlin as do most type 1 patients. We are eager to see the Symlin data in the type 2 study in the second half of 2006. Through the market research, we learned that the most important differentiators for HCPs using Byetta were its unique mechanisms and associated weight loss. The market research showed that doctors were 10 times more likely to prescribe if they had been educated on its use. The latter will be key against DPP-IVs, which benefit from non-injection (as well as having some significant incretin education work done by Amylin!). It appears, really, that many PCPs are just starting to learn about Byetta. Since we know it takes time to learn (remember, they're all stretched thin), we're enthusiastic about the opportunity.

Amylin and Medco signed an agreement that should boost sales through mail order, by far the fastest-growing channel. While the margins are a bit lower, the volume impact will be a nice positive, in our view. Amylin is still being fiscally conservative; for example, it will selectively increase promotional spending in 2006, but it isn't going overboard.

As everyone knows, in diabetes, reimbursement is always key. Over 90% of people covered by managed care have access to Byetta and Symlin, which has happened remarkably fast, though novel compounds typically have a much easier time in gaining coverage- 30 percent at tier 2! We can't wait until the monotherapy study is in full swing: with this data, we believe Byetta will begin to be used earlier in disease progression.

The final tidbit of good news – in 2006, Amylin's specialty sales force is increasing from 56 to 76.

BECTON DICKINSON F1Q06 and JPM - Diabetes products as 'major revenue drivers' – thanks, Amylin!: BD reported its first fiscal quarter January 26, and we learned that blood glucose monitoring sales reached \$23 million for the quarter and that the company remains to be on track to report \$115 million in this area for 2006. During Q&A, the company shared some interesting perspective about the market and the move to pens, which has been very delayed in the US, compared to Europe. Management emphasized that Byetta and Lantus have been key growth drivers for this – when Amylin and Sanofi do well, of course, BD benefits. There doesn't appear to be limits to growth as we learned the company had made more plans to increase pen needle capacity – as we have mentioned before, pen needles are a significant contribution to growth for the company. Although Symlin is a much smaller product, we also note that BD benefits from Symlin growth as well, which should become more noticeable over time. To file under diabetes tangents: we know many patients who use far more syringes with Symlin, because it's harder to reuse the syringes (as patients do all the time with insulin) – the rubber at the top of the Symlin vial is much tougher to break through and the needles seem to dull immediately. A few words on BD's presentation at JPM - Vincent Forlenza, President of Becton Dickinson (BD) Biosciences, gave an overview of the company and its three divisions (Medical, Diagnostics, and Biosciences). Although

diabetes, which is the second largest unit within BD Medical, was briefly mentioned, it was *very* interesting that blood glucose monitoring and insulin delivery were described as two of the major revenue growth drivers for BD Medical – glucose monitoring to date has been challenging to jumpstart, but clearly the business is benefiting from a strong market. And the company is probably inspired by other aspects of its diabetes business, including syringes and pens, which are moving extremely well, as noted.

BMS 4Q05 - Saxagliptin benefits from 14% 4Q R&D spending increase: We learned no real news on BMS and diabetes/obesity in the BMS 4Q05 comments January 25. Nothing was said about muraglitazar or Saxagliptin in the press release, although the call included a generic statement about how Saxagliptin is one of the late stage products that BMJ continues to invest in and is one contributor to the double-digit growth in the R&D budget. R&D spending rose 14% in 4Q05, by the way. On muraglitazar, executives says they "continue to evaluate their options" but certainly at this point, it seems likely to be shelved: 1) first, of course, it sounds like FDA would require more studies that would take at least a couple of years, and since the data haven't been stunning, it's hard to argue that the commercial opportunity justifies a major (further) investment. And it's far from a home run, especially with Byetta new to the market, and there must be countless competing priorities for R&D resources. 2) The other question is who would help market this to PCPs with MRK having dropped out and the product having a tainted feel.

ABBOTT 4Q05 – Overachieves on \$1.0 billion sales milestone: Abbott reported January 25 its 4Q05 earnings, highlighting that Abbott Diabetes Care has exceeded the \$1.0 billion milestone mark in revenue. The company's remarks on the Navigator (continuous monitor) indicated a very positive outlook on this device, suggesting it's pleased with the clinical trial results, now finished. The product is expected to be approved and launched later this year.

Abbott executives cited the strength and success of ADC on multiple occasions during the call. The company announced that '05 sales grew 34.8% while 4Q05 sales rose 18.1% from 4Q04. Management indicated that the company currently has 20% market share in this industry. Abbott expects its new Freestyle Connect blood glucose monitor, which received FDA approval in 2005, to help continue its success in the hospital. In support of this, an executive said that it will be the fastest monitor available, generating results in 15 seconds, and requires the smallest blood sample of any current monitor. In other related diabetes/CVD/obesity results, Abbott said that it has ongoing trials looking at combination therapy possibilities for Tricor with statins – look for the data later this year. In response to a question concerning what products/divisions of Abbott the street may be underestimating, the company said it felt that public expectations should be higher for Abbott Diabetes Care, among just a couple of others explicitly mentioned (rheumatoid arthritis treatment Humira and fenofibrate Tricor).

J&J 4Q05 – Achieving \$1.9 billion in LifeScan sales and looking forward to continuous: JNJ LifeScan reported 4Q05 earnings January 24. Results were definitely weaker than expected, with worldwide sales up just 5% for the quarter – results haven't been this weak for LifeScan since mid-2003, when sales fell 7%. Since then, global sales have always increased at least 10%. While this quarter was a tough comparison in that fourth quarter 2004 sales had risen a whopping 19% (up 12% domestically and 28% internationally), it's clearly getting very tough to sustain such high historic growth rates. This partly reflects a higher base of sales but also suggests other greater pressures as well on many potential fronts, including competitive, regulatory, reimbursement, etc. What's notable is that neither LifeScan's US nor international sales were *extremely*, extremely strong, as we usually see. Historically, LifeScan sales at times were weak either in the US or internationally, but almost always *either* the US or international sales were very strong and could bolster the other. This is actually the first quarter in nearly five years (since the second quarter of 2001) where both domestic and international sales growth was under 10%. Still, reaching \$1.9 billion in sales for the year is a major achievement. LifeScan will benefit from pump sales starting in 2006, and the extra revenue will certainly benefit the area. The \$100 million in sales from

Animas would add about five percentage points of growth for 2006. Detailed notes on the quarter included the following:

- Medical Devices and Diagnostics (MD&D) sales were \$19.1 billion in 2005, with 12.5% operational growth in 2005. Profit contribution from (MD&D) has increased more than threefold. Highlights related to diabetes and obesity from the call;
- Lifescan achieved operational growth of 5% in 4Q05 as compared to the same period in 2004. This growth was led by U.S. growth of 8%.
- One Touch Ultra was the major growth driver of both U.S. and WW sales
- One Touch Ultra achieved 34.9% script share as of 3Q05 - we look for this to strengthen further when the new Ultra is introduced this year.
- The only comment about the very weak international growth was that growth outside the U.S. was negatively affected by sharp reductions in retail trade inventory.
- CEO Bill Weldon highlighted the “alarming” increase in the prevalence of diabetes worldwide.
- Currently J&J is focused on episodic glucose monitoring with its One Touch line. However, J&J is moving from measurement towards “broad management of the entire diabetes spectrum.” (It began this at the summer 2005 meetings, when it started positioning as “not just a monitoring company.”)
- LifeScan is introducing “transformational technology” to develop diabetes management solutions that will transform patient care, “bringing affordable BG monitoring to new geographies.” Its strategy is focused on continuous monitoring.
- Weldon highlighted the pending acquisition of Animas, which will “broaden [J&J’s] reach in diabetes management” as one of J&J’s key acquisitions.

He also briefly mentioned obesity as one of the “best opportunities for significant and sustainable growth” that J&J is pursuing, along with nutrition and colon cancer. Splenda was also touted as an important alternative for patients struggling with diabetes and obesity. We didn't hear anything about Obtech, its obesity device company. J&J will hold a full-day review of its MD&D segment in September 2006 – we look so forward, especially as more will undoubtedly be said on the exciting new insulin delivery front.

PFIZER 4Q05 – Ready to inhale: Pfizer reported its 4Q05 earnings January 19; the company’s press release highlighted Exubera, an “innovative diabetes product candidate,” as an example of its continuing investment in future growth – this followed a recent announcement on the \$1.3 billion purchase of Sanofi worldwide rights (and the insulin production facility in Frankfurt) to Exubera. Exubera had at that time been recommended for approval by the FDA advisory committee and for marketing authorization in Europe. We had been thinking the company had been sounding optimistic and confident – indeed, they had! We will look forward to covering Pfizer and Nektar in significantly more depth in coming quarters!

NOVARTIS 4Q05 – Ready DPP-IVs: Novartis reported 4Q05 results January 19, announcing that Vildagliptin, LAF 237, has been christened Galvus. Galvus is on track for FDA filing later this quarter, with a launch expected early- to mid-2007. The company moved up European filing into 2006, and there is a question about whether they need two-year SFU head-to-head data – it sounds like they do not. Basically, our view on Galvus is that the drug isn't a great monotherapy drug versus metformin but is good versus Avandia (while TZDs are being used more as first-line therapy, some HCPs still avoid because of weight gain and edema and safety concerns including congestive heart failure) and it is a solid add-on drug. Then, the trouble with *that*, though – if the efficacy isn't that much different from Metformin, we're not sure how many payors are going to want to fund fancy new drugs that really only work in combination therapy when the age-old safe generic works pretty well itself (remember that Galvus failed the non-inferiority to Metformin last year). The TZD data did look good: A1C dropped ~1.8 for both Galvus and Avandia, though no information was given regarding baseline A1C. Management focused on the fact that there was no weight gain, no edema, and better tolerability in this trial. Galvus can be dosed once *or* twice daily and is administered orally. Novartis is looking at a fixed

dose combination of Galvus and metformin; the drug is weight neutral. Management emphasized that, logically, the more severe the patient population, the better the drug works.

GlaxoSmithKline (GSK)'s – OTC panel comes in as expected: On January 23rd, a joint US FDA advisory committee voted 11 to 3 in favor of approving GSK's orlistat 60mg for over-the-counter use in the US. If the FDA follows the recommendation made by its joint Nonprescription Drugs and Endocrinologic and Metabolic Drugs Advisory Committee, orlistat would be the only FDA-approved over-the-counter (OTC) weight-loss treatment in the US. The FDA will probably but not certainly follow the panel's advice. How big is this market? As the only drug that will reduce obesity (regardless of label), and because we know Americans are stupid about taking drugs they don't need to take, we imagine this could be significant – but as big as the president of GSK's North American consumer health division, George Quesnelle, seems to think. He says that five to six million Americans would purchase OTC orlistat if it is approved by the FDA. Each tablet would cost about 60 cents, and patients would take three to six tablets daily. That's a multi-billion dollar market, which we think is extremely optimistic – though we're always shocked that Xenical still brings in as much as it does, given the side effects.

GSK bought the marketing rights from Roche to take orlistat over the counter and would market OTC orlistat under the brand name Alli. In the case of FDA approval, advisory panel members urged GSK to study Alli when it's on the market to monitor its use by consumers and determine the long-term effectiveness of the drug, as most studies of orlistat lasted no more than six months. GSK has recommended that OTC orlistat be used for six-months in conjunction with a diet and exercise program.

A six-month GSK-sponsored study showed that overweight or obese patients taking Alli along with a program of diet and exercise lost 4-5 lbs more than patients on diet and exercise alone. In longer-term studies of Xenical (120 mg orlistat), however, patients tended to regain lost weight within two years. There are also concerns that patients taking orlistat could develop vitamin deficiencies, as the drug partly blocks the absorption of fat-soluble vitamins. GSK recommends that patients take a multi-vitamin once a day two hours before or after taking orlistat, but consumer-use studies have shown that less than half of consumers took the vitamins as directed. Much of the support for approval of OTC orlistat seems less related to the benefits of the drug and more related to the fact that it is better than the countless, unapproved alternatives on the market. FDA advisory committee member Neal L. Benowitz, MD, expressed concerns that patients would regain lost weight after stopping orlistat treatment, yet he recommended approval of the drug anyway, partly because making orlistat available over the counter could drive patients away from the many potentially unsafe products that are available.

The following snippets are based on watching multiple presentations at JP Morgan's 24th Annual Healthcare Conference in San Francisco earlier this month.

INSULET at JPM – First corporate presentation draws SRO crowd: Duane DeSisto, CEO of Insulet, presented for the first time at a corporate conference – excitement abounded. The room was big and close to standing room only. DeSisto alluded to the *NY Times* "Bad Blood" series that ran recently, noting that it drove home the need for treating diabetes differently in the US. He emphasized that there is no substitute for insulin, that physiologic delivery is best, and that in general, earlier, more aggressive therapy is needed. He then spent time on the management team and the medical advisory board, which includes luminaries like Drs. Bob Sherwin of Yale, Fran Kaufman of UC Children's, Lois Jovanovic of Sansum, Steve Edelman of UCSD, and John Buse of UNC. Fabulous!

Insulet's Omnipod was launched in late October – we believe the pump is enjoying early commercial success and that this breakthrough product will in time do much to expand the current pump market. What do patients like so much about the pump? No infusion set tethers; more discretion; easy programming, easy set up and insulin filling process, stellar user interface features, absence of pain associated with killer

automatic insertion system, fewer scars, fewer air bubble problems, and better insulin absorption. This long list was fairly convincing, especially as it was followed by in-depth information on Insulet's market research with 162 HCPs and 2,756 patients. When we think of smash product launches for diabetes products in the US, we always think of Lantus – it was simple, and simply sold (the old “one shot a day, one pill a day” marketing campaign will be interesting to watch evolve as Apidra is launched ...). Insulet will benefit from marketing simplicity, as the Omnipod is exactly that – simple to program, fill, wear. This is a big deal. That said, by no means do we believe *everyone* will rush to get Omnipod – some patients like traditional pumps just fine, thank you. The nice thing for Insulet is that everyone doesn't *have* to switch. We believe what the company could get in new users alone (for example, people who considered but never made the transition to a traditional pump) would be a stunning success, as long as reimbursement and manufacturing automation and customer service are all taken care of, and we know that with such a deeply experienced management team, this won't be a problem.

Another major part of DeSisto's talk was that its product was a platform for the continuous sensor. He clearly believes this will be important, but not in the very near term. Specifically, he said that a sensor would be relatively easy to incorporate, and that from day one, this had been a priority. He did emphasize insulin delivery was the primary focus for now.

The intellectual property was characterized as robust, and it was pointed out that Insulet hired an IP lawyer as the #25 employee! IP is clearly key in this area. He said the company has 12 issued patents, one licensed patent, five allowed/allowable US applications, 30 pending US applications, and a corresponding number of foreign patent applications filed and issued in Australia, Canada, China, Europe, and Israel.

On the revenue front, DeSisto said they had a few hundred patients now and would have a few thousand in a year. He said they were ready to go “head to head” with others in the market. On an excellent side note, he also shared that they had been approached to do other drugs and had already made a wholly owned subsidiary – but the core Insulet was a diabetes management company.

On reimbursement, DeSisto said the company has received reimbursement codes and are working on getting reimbursement throughout the US. Costs were discussed at some length – the motor was described as very low cost, about \$0.25 each. Current costs are unknown, and we expect line automation will bring costs down considerably.

MEDTRONIC at JPM - Prepares for launch of sensor-augmented pump: Art Collins, Chairman and CEO of Medtronic, gave an overview of the company, emphasizing Medtronic's focus on innovation for chronic diseases and large, under-penetrated markets. R&D is Medtronic's largest expense category, with more than \$1 billion spent this year, and R&D is growing faster as a percent of sales than revenue growth.

Although nothing new emerged on diabetes, the disease was one of the four therapeutic areas that Collins highlighted (not surprisingly, the other three were cardiac rhythm management, spine, and vascular). Over the next three years (2005-2008), Medtronic's three largest businesses – CRM, spinal, and diabetes – are expected to generate >85% of total company growth. Medtronic was described as “the leader” in pump and glucose monitoring technology, and Medtronic's diabetes business has been growing in the “high teens,” driven by the “epidemic” in this country, particularly in the “younger generation.” Recently, as we knew, there has been a limited launch of the Guardian RT continuous glucose monitoring system, though few details were offered. A sensor-augmented pump system will be launched in FY 2007 (which begins in May 2006). Collins appeared confident on this front and didn't expect to need a panel meeting. As for clinical trials, the STAR 1 trial has been completed and the STAR 2 trial, comparing the benefits of sensor-augmented and pump therapy to multiple-daily injections, is currently enrolling patients. Over the next several years, Medtronic intends to continue to enhance its pump and sensor technology toward the ultimate goal of creating a closed-loop system that operates like an artificial pancreas.

MERCK at JPM - Tight-lipped on diabetes: Merck's presentation focused mainly on broad strategic planning and cost-cutting measures to be implemented over the next five years. The company shouldn't be expected to say a lot about diabetes, and it didn't. Like many of its competitors, Merck is concentrating on multiple research areas, including diabetes and obesity as two of its nine priorities. In a brief discussion of these areas, CEO Richard Clark recognized both diabetes and obesity as two of the fastest growing diseases, saying that diabetes would be a key part of Merck's focus as it moves forward. Januvia (MK-0431) was mentioned on two occasions as a key innovation product, one that Clark expects to help drive growth while Merck changes its business model. He noted its potential to lower blood glucose levels and alter the long-term effects of diabetes. He expects Januvia to be filed with the FDA in 2006. Two other pipeline products relating to diabetes (MK-0431A) and obesity (MK-036) were mentioned in a chart of all the products Merck is currently developing. MK-0431A is currently in phase 3 - it's the Januvia-metformin product - and MK-036 is in phase 2b.

ALKERMES at JPM – “A freight train of forward inertia”: Isn't that the best line you've ever heard? So regarding the company's two diabetes programs –LAR and AIR insulin – CEO Richard Pops said that there was “a freight train of forward inertia in these programs now,” with the goal of helping type 1 and type 2 diabetics enjoy better lives over the long term. Alkermes is currently on the threshold of profitability and growth. Regarding AIR pulmonary insulin, the company is “exceedingly excited about this particular dosage form.” Since there is a significant need for simpler insulin treatment regimens, patients are the ones who are pulling this product forward. AIR insulin also has the potential to improve therapeutic outcomes. To date, the following progress has been made:

- Phase 2 results were presented at the 2005 ADA and published in *Diabetes Care*, demonstrating that AIR insulin provides A1C control comparable to injectible insulin and that 80% of patients prefer inhaled insulin to mealtime injections.
- Phase 3 registration program is currently underway, consisting of a 24-month study in 400 non-smoking type 1 patients and a 12-month study in 600 type 1 and type 2 patients with asthma or COPD.
- Additional efficacy studies in “special populations” are planned for 2006.
- A two-year safety study was initiated in 2005.
- Large-scale manufacturing is in place.
- Easy-to-use inhaler design has been finalized – it is a small, disposable inhaler that is replaced every month.

Re: LAR (Amylin's next-gen Byetta): Pops hailed this as “*one of the most exciting new drugs for the treatment of type 2 diabetes ever.*” A phase 2 multi-dose study was completed and interim results were reported in August 2005. Although the data set was small, “*results at 15 weeks showed both doses were well-tolerated and there were dose-dependent improvements in A1C and weight.*” He reviewed data showing that in the high-dose group compared to placebo, A1C improved ~2%, 12 out of 14 patients achieved A1C ≤ 7% compared to none in the placebo group, fasting glucose was reduced ~50 mg/dl, and there was an average nine-pound weight loss. The most common side effect was nausea. The follow-up period has now been completed, and no new safety concerns were observed during the follow-up.

Pops said the next clinical step is the initiation of a long-term study evaluating LAR safety and efficacy. The study is expected to start in 1H06, and it will be an open-label, randomized trial that includes a Byetta twice-daily reference group. The efficacy end-point will be reduction in A1C. He closed by noting Alkermes's goals for 2006 include helping Amylin prepare its commercial facility for LAR, supplying AIR insulin for phase 3 registration studies, and presenting new data at ADA for AIR insulin and LAR.

ARENA at JPM - Grooving on work in diabetes and obesity but no real news: Arena gave no news of its diabetes or obesity programs. As a reminder, Arena has under study two preclinical compounds targeting the 19AJ receptor in the pancreas. These compounds target a receptor preferentially expressed in

the beta cells that may lead to increased levels and activity of intracellular factors involved in beta cell preservation, a focus of drug companies of late. Any drug that halts the progressive nature of type 2 diabetes would be in high demand. Arena has noted that its compounds may be delivered orally and are glucose dependent, and the company has partnered with Ortho-McNeil on these two compounds. Arena's obesity compound, APD356, is furthest down its pipeline and selectively targets the 5-HT_{2C} serotonin receptor. Arena announced positive results of a phase 2b trial in December, with highly statistically average weight loss of 7.9 pounds over 12 weeks for the 20 mg group.

BIOVAIL at JPM - Combo drug to combat compliance issues? Dr. Douglas Squires, Biovail's CEO, gave an overview of the company and its technologies, explaining that Biovail currently markets one diabetes product, Glumetza, a once-daily metformin for type 2 diabetes. Glumetza received Canadian approval in May 2005 and was granted three years of Hatch-Waxman exclusivity. It was launched in November 2005. Biovail is also pursuing extended release and combination product opportunities related to diabetes, including an insulin sensitizer/biguanide combination and a hyperlipidemia/diabetes combination. However, diabetes products did not rank particularly high on a priority list of R&D projects based on the company's commercial assessment framework.

EMISPHERE at JPM – Generating phase 2 data for oral insulin: Dr. Michael Goldberg, Emisphere's Chairman and CEO, gave an overview of the company, noting that Emisphere focuses on developing oral formulations of injectable drugs, including insulin. The company believes the oral insulin is a \$6 billion market (based on 2004 WW sales of injectable insulin) and has the "*potential to revolutionize diabetes treatment.*" It was said that currently, only 27% of type 2 patients on insulin in the US get to their target A1C level of <7%. Emisphere believes that injectable insulin therapy fails for several reasons, including patient adherence/compliance, hypoglycemia and weight gain concerns, non-physiological pharmacokinetics, and prescription as a "last resort" therapy. Emisphere said that severe hypoglycemia and weight gain "may be more related to the way [insulin] is dosed and not to the product." The company also believes that injectable insulin fundamentally targets the wrong tissues (muscle and fat instead of the liver.) In contrast, Goldberg emphasized, oral insulin follows a physiological route with delivery into the portal circulation. As a result, it was said that Emisphere believes that oral insulin could be a first-line fixed-dose therapy. In 2005, Emisphere initiated a "make-or-break" phase 2 study of oral insulin, developed significantly improved tablet dosage forms, initiated clinical studies to evaluate new formulations that "dramatically increase bioavailability," and initiated clinical studies to evaluate the mechanism of oral insulin in humans.

A phase 2 in 120 type 2 patients failing monotherapy was initiated on November 15, 2005. This is a 90-day, double-blind, placebo controlled study following a three-week run-in phase. The study is being conducted at six centers in India (India!). Subjects on metformin are randomized to active therapy (tablets each containing 150 IU of insulin + 80 mg of carrier + metformin) or control (placebo + metformin). Efficacy endpoints include A1C, glycemic control, and weight change. Safety endpoints include hypoglycemic episodes and insulin antibodies. There are four treatment arms: 1) Two insulin/4-CNAB tablets 4x/day; 2) Two insulin/4-CNAB tablets 2x/dy + 2 placebo tablets 2x/dy; 3) One insulin/4-CNAB tablet + 1 placebo tablet 4x/dy; and 4) Two placebo tablets 4x/dy. To date, 40% of patients have been enrolled and there have been no hypoglycemic events. Data from this trial are expected in mid-2006. Based on this data, the company hopes to partner oral insulin on "competitive terms." In addition to oral insulin, Emisphere is also developing a number of oral drugs for obesity, including GLP-1, rhGH, and PYY. Dr. Goldberg believes that an oral GLP-1 "*principally focused on weight loss, but also potentially usable in diabetes*" should be "*very straightforward and relatively easy for [Emisphere] to do.*" This is a confident crowd – personally, we feel like we've been watching and waiting for products for a million years, but the products are usually late or not up to promises, so for now, we'll monitor this one.

—by *Katelyn Gamson, Cindy Glass, Nate Freese, Rachael Hartman, Erin Kane,*

4. Scrutiny on diabetic care in hospitals raises hopes for improved treatment

Continuous Glucose Monitoring is Key for Normal Glycemia in ICUs

Diabetes care in hospitals will receive new scrutiny this year (see preview of AACE meeting on page 20), as recent studies have underscored both the shortfalls and opportunities in this area. That bodes well for patients who, ironically, often receive suboptimum care in hospitals. The challenge is to convince hospital administrators to spend money to improve treatment and then to implement a plan to achieve that goal.

We think momentum is heading in that direction, assisted by the prospects of breakthroughs in continuous glucose monitoring. We believe the shift toward tighter control in hospitals could easily increase the size of the current hospital-monitoring market from under \$400 million a year to at least double that size, and continuous monitoring could play a major role, particularly if it can reduce the burdens on nurses.

These issues were discussed in detail at the Society of Critical Care Medicine's 35th Critical Care Congress in San Francisco on January 7-11. The meeting typically flies under the diabetic radar screen, but a relatively strong emphasis this year on the disease underscored the scope and severity of the problem. Three things stood out for us:

- Data confirm that tight glycemic control in hospitals saves lives and money, which is now drawing attention from hospitals; and healthcare professionals clinging to "sliding scale" dosing are losing ground;
- At least one company, OptiScan, is closer with a glucose-monitoring device than we anticipated – the company forecast that the product would be on the market a year from now, far ahead of its large-cap (as well as privately held small-cap) brethren;
- A recent nurse survey quantified the costs of the additional work for keeping patients in tight control and identified why such efforts are resisted.

Mediocre care in hospitals is a poignant commentary on the state of overall diabetic care in America. Hospitals should be ideal settings for tight glycemic control, as traditional barriers to treatment – patients' lack of knowledge, supplies, or proper diets – are eliminated. But studies have continually shown that hospitals have significant room for improvement.

Five years ago, Dr. Greet Van den Berghe published a landmark ICU study. In a randomized, prospective, controlled trial of 1,548 patients, improved control led to a decrease in ICU mortality from 8.0% in the conventionally-treated group to 4.6% among those on intensive insulin therapy, while comorbidities declined significantly as well. At the San Francisco conference, Dr. James Krinsley of the Mayo Clinic, a highly respected leader in this area, shared new clinical data. In his ICU, researchers have examined the relationship between glucose control and mortality. Evaluating 4,588 patients (2,655 from October 1999 to February 2003; 1,933 since February 2003), he found a strong relationship between increasing glucose levels and hospital mortality. The initial glucose goal was 80 to 140 mg/dL, but the new target range is between 80 and 125 mg/dL. Patients with mean glucose levels of 70 to 99 mg/dL survive at a rate double of that predicted by the APACHE III model. Dr. Krinsley noted that the nursing staff felt more comfortable with the 80-125 mg/dL goal, saying, "Many are paralyzed by this idea of 80 to 110."

Importantly, he recommended that hospitals begin by choosing a target level with which their nurses are comfortable, rather than creating a more stringent goal that will not be met.

Dr. Krinsley also presented unpublished data from cost analyses of two pivotal ICU studies. In the Van den Berghe trial, researchers quantified the cost of the ICU days, mechanical ventilation, antibiotics,

vasopressors, inotropes, and transfusions, and they found that that tight glucose control generated a savings per patient of \$2,638, with a mean length of stay of 6.6 days. (This will be published by *Critical Care Medicine* in the first part of this year.) In a separate trial that also showed the benefits of good control in a hospital, a cost analysis concluded that the effort saved \$1,560 per patient, with a mean length of stay of 3.4 days. (This will be published later this year in *Chest* by Krinsley et al.)

The principal obstacles to better care in hospitals are that glucose monitoring is time consuming, nurses are in short supply, and providers fear hypoglycemia. Dr. Krinsley identified the development of continuous glucose monitoring as a possible solution to improving hospital care. Dr. Krinsley himself was the lead author of a study on OptiScanner, whose results were presented on a poster at the conference. OptiScanner is a continuous glucose-monitoring device that uses mid-infrared spectroscopy to monitor glucose and contains an algorithm to correct for potential drug interference in its measurements. The poster presented evaluations from two different OptiScanner trials, and the researchers concluded that the device could provide a continuous stream of data in the ICU that could help intensify insulin treatment and blood glucose monitoring.

The study indicated that the OptiScanner is precise and impressively accurate; although identification of drug interferents is currently accomplished manually, this should be automated in the final product, which may not sound trivial, but which we think is actually pretty trivial. OptiScan management said during the poster session that the company expects the OptiScanner to be on the market by next year's conference in mid-January, suggesting that a 510-K will likely be filed in the near-term.

Glucolight Corporation was the one other company with a poster in the glucose-monitoring area. It is currently developing a continuous, non-invasive glucose monitoring device for hospitals, using Optical Coherence Tomography (OCT) technology to measure changes in blood glucose levels through changes in the dermis of the skin. We found the data it presented encouraging and expect that Glucolight is now at work developing a continuous monitoring device, including the development of a real-time data-display algorithm and a more refined calibration system that requires less than a 60 mg/dL spread, which isn't always easy to get with hospitalized patients. No timing was given on plans for testing in the ICU but the company certainly appears very focused.

It's noteworthy that OptiScan and Glucolight were two of only four companies with a visible presence at the conference (Glucon and Roche were the others), and three of the four companies is private and small. Underdogs often take the initiative in forging into new markets with new products, but we believe the rest of the larger players are looking at the hospital market with great interest and are working behind the scenes to swoop in – perhaps by following, perhaps through acquisition. The options seem endless, indeed, for this technology that can do so much good for a group that is so needy.

Finally, Dr. Daleen Aragon presented results from a survey of 122 nurses on their response to tight glycemic control. (The survey was funded in part by Glucon.) Direct observation showed that each nurse had his or her own technique for BG monitoring and administering insulin – with 32 potential steps in the process. The mean time to do this, including documenting the act, was 4.72 minutes. A survey showed relatively strong support for the statement that “BG monitoring is too much work.” Sixty percent of respondents said that “tight glycemic control” is too much work, while 70% said that “tight glycemic control takes too much time.”

The nurses worried that frequent or hourly glucose tests could cause infections (not likely) or patient pain (which usually isn't true). A majority of nurses recognized that normal glucose levels helped with patient outcomes, while virtually all concluded that an automated monitoring system was necessary to reduce their workload. The study also showed that at a 58-bed critical care unit in Orlando that is a level-one trauma center and has a wide range of patients, the cost of tight monitoring for one year was \$244,424.

Dr. Aragon concluded that our current method of monitoring is expensive and time consuming and that an automated or continuous system is necessary to achieve tight glycemic control in hospitals. Even if medical device companies perfect such a system, hospitals will still need to be convinced to purchase it. That will be a separate hurdle but one we hope to face in the near future.

– James S. Hirsch and Kelly L. Close

5. Conference Preview: Improving Inpatient Diabetes Care: A Call to Action Conference, Washington DC, Jan. 29-30

The American Association of Clinical Endocrinologists (AACE) and ADA will be hosting “Improving Inpatient Diabetes Care: A Call to Action Conference – Consensus Development Conference” January 30-31 in Washington, DC. We wrote about this in our blog as a conference not to miss on January 3 – the conference is already sold out, and our pens are poised, we *so* are geared up for this meeting.

The way the conference is organized is fascinating: participants will work through seven questions, beginning with, “Does improving glycemic control improve clinical outcomes for patients with inpatient hyperglycemia?” (and we all know the answer to that question is an overwhelming yes!) and working toward, “What are the areas needing further research?” We see this final question as key, along with question four—“What are the systematic barriers and challenges to improved diabetes management?” We hope that question five— “What are effective strategies for achieving improved management in hospitalized patients?” — will suggest a path for improvement.

Dr. Etie Moghissi will deliver the first presentation on “Current State of Inpatient Diabetes Burden and Care, and the Goal of the Conference,” followed by an all-star first session with legendary Dr. Greet Van den Berghe (“Data Derived from Surgical and Medical Intensive Care Units”) alongside fellow all-stars Drs. Anthony Furnary (“Review of Data in the Cardiac Surgery Population”) and Irl Hirsch (“Data from Patients in Cardiac Care Units and in Non ICU Populations”). Session two on cost will feature Dr. Thomas Balcezak on “New Clinical Initiatives: the View from Hospital Administration,” Dr. Bruce Lawrence on “The Financial Benefits of Changing Inpatient Diabetes Care,” and Dr. Christopher Newton on “Financial Implications of an Inpatient Diabetes Program.” We’re looking especially forward to this session after seeing some compelling data at the Critical Care Conference on how hospitals can simultaneously save money and improve patient outcomes.

At the conclusion of the conference, the participants will write a conference statement. The position statement coming out of the 2003 meeting on inpatient diabetes answered seven slightly different questions, concluding that “*data from multiple studies confirm that hospitalized patients with hyperglycemia suffer significant excess mortality and morbidity, prolonged length of stay, unfavorable post-discharge outcomes, and significant health care costs*” and recommending “*early detection of hyperglycemia in the hospital and an aggressive management approach to improve outcomes.*” We will be reporting from DC on our blog and in the next edition of DCU.

—by Erin M. Kane and Kelly L. Close

6. Focus on Obesity: from the AHA obesity conference to a Memphis town hall meeting AHA Obesity, Lifestyle, and Cardiovascular Disease Symposium January 18-20, 2006, Washington D.C.

The AHA convened this conference in mid-January on the growing obesity epidemic: why it is so important and how lifestyle changes must play a role in the fight against it. The conference focused

primarily on three dimensions of obesity: 1) the health risks; 2) how to promote more healthful diets; and 3) the role of physical activity in preventing overweightness and obesity. Although the conference had many sponsors from the industry, including Amylin, Merck, Novartis, Pfizer, and Sanofi-Aventis, very little emphasis was placed on the role of the healthcare and insurance industries. Below are some of the themes from the conference:

On general lack of drug focus: There was almost no mention of the potential role of drugs as treatments for obesity, with the exception of one presentation by Dr. Susan Yanovski of the National Institute of Diabetes and Digestive and Kidney Diseases at the NIH. This may reflect that many of the presenters are pessimistic about the reimbursement potential for obesity drugs, whose purposes are thought to be “cosmetic.” Several doctors, including Dr. Eckel, made brief references to the dim reimbursement prospects for drugs whose primary indication is obesity. In addition, the conference placed a strong emphasis on helping individuals assume personal responsibility for lifestyle changes, as new weight-loss drugs could decrease a person’s motivation to eat more nutritiously and exercise more.

On Xenical, Meridia, and Acomplia: Dr. Yanovski discussed the two current obesity drugs on the market – Xenical and Meridia – along with Acomplia, currently under FDA review. She was fairly positive on the benefits of each (which shocked us for Xenical and Meridia, due to their disturbing side effect profiles), although she believes they are all capable of inducing only moderate weight loss. Although she reviewed the side-effect profiles of each drug, she did not emphasize them. In general, she seemed very interested in learning more about Acomplia, even asking anyone in the audience if they knew more!

On Byetta and Symlin: Dr. Yanovski concluded with a brief mention of off-label use of Byetta and Symlin as weight-loss drugs. Although she stressed caution in using these drugs off-label, she was generally optimistic about their use, especially with patients who have the drugs’ primary indications.

On obesity and health risks: The association between obesity and negative outcomes such as diabetes, metabolic syndrome, and cardiovascular diseases was another point of relative consensus. Several presentations cited the many studies supporting these associations. Therefore, it was surprising when Dr. Eckel appeared to downplay the health risks of obesity, citing a study that reducing BMI from 30 to 24 only improves life expectancy by four months while going from 35 to 24 improves life expectancy by one year. In response to an audience question, Dr. Eckel was also hesitant to classify obesity as a “categorical risk factor” like diabetes and smoking; rather, he preferred to call it a “modifiable risk factor.”

On dieting debates: Much of the conference could be sub-divided into mini-debates over the merits of low-carb vs. low-fat diets, the value of glycemic indexing, and the relative importance of diet vs. exercise. In general, there were few, if any, resolutions on these issues – presenters on both sides of each issue cited numerous studies and data in support of their arguments but spent relatively little time engaging the counterarguments to their position.

On flawed studies: One common explanation for the conflicting studies on diet and physical activity was that these are difficult areas to study scientifically; and thus, many studies use flawed methods or reach misleading conclusions. For example, Dr. Sunyer criticized Dr. Liu’s presentation about the benefits of glycemic indexing because his evidence was primarily based on extrapolating data from patients with diabetes to the rest of the population.

On the all-important calorie: The importance of restricting caloric intake to prevent weight gain and/or induce weight loss was a point of near-unanimous consent. Almost every diet plan at the conference was defended on the basis that it reduced caloric intake, while presentations about the importance of physical activity also stressed the need to limit energy intake while increasing energy expenditure.

On whether there is an obesity “defect”: The issue of whether a genetic defect predisposes people to obesity was a hot topic. Dr. Bouchard first raised the idea by saying he believes that obesity is unavoidable in about 2% of the overall obese population, due to a genetic defect. Critics of this position could be divided into two categories—those who disagreed on a scientific basis and those who were concerned that such a theory might discourage patients from fighting their obesity. Dr. Bouchard responded by saying that, “unfortunately, there *are* defects – that’s exactly what they are, people who have them become obese no matter what.”

SHAPING AMERICA’S YOUTH (SAY) TOWN MEETING

January 21, 2006, Memphis, Tennessee

This meeting was the first of its kind in a series of town meeting style conferences, to be held across the country, to promote nationwide efforts to improve our children’s eating and exercise habits. Convened by Shaping America’s Youth and hosted by the Healthy Memphis Common Table, the meeting brought together local residents, students, and healthcare professionals to discuss the increasing prevalence of obesity in Tennessee and the nation. We report that the meeting ran smoothly, enthusiasm was high, and participants remained engaged in the issues throughout a long day of speeches and discussion – it clearly exceeded many expectations!

A number of local and national leaders from the healthcare and political arenas spoke at the conference, including Tennessee Governor Phil Bredesen, leading pediatric endocrinologist Fran Kaufman, Assistant U.S. Surgeon General Wood Kessel, and Shelby County Mayor A.C. Wharton. Mayor Wharton’s speech was particularly invigorating...literally...as the 61-year-old did 50 push-ups on stage, in an impressive display of physical fitness. Several other figures sent video-recorded messages that were broadcast at the conference, including Senate Majority Leader Bill Frist and U.S. Surgeon General Richard Carmona.

Participants spent roughly half of the meeting in small groups discussing key obesity issues. During the morning each group was asked to come up with lists of the barriers that face families, communities, and states in their efforts to improve the eating and exercise habits of our nation’s youth. Much of the afternoon was then spent brainstorming on strategies for overcoming these barriers and promoting healthier lifestyles.

Another key goal of the conference was to gather data on participants’ attitudes toward obesity and how the problem should be addressed. The conference used electronic polling equipment to record participants’ responses and displayed them at the conference in real-time. We look forward to seeing the full results, which should be posted soon at <http://www.shapingamericasyouth.com>

While participants and organizers alike seemed pleased with the meeting, the ultimate test will be whether the ideas from it can be translated into specific actions in the community and beyond. The event has already succeeded in drawing some outside attention, as various stations (CNN, etc.) ran news stories the next morning.

— by Nate Freese

7. Literature Review: Scientists discover gene for type 2

Grant, Struan F.A. et al. “Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes.” *Nature Genetics* 15 January 2006

Overview: Researchers from Iceland, Denmark, and the University of Pennsylvania report in *Nature Genetics* on January 15 that they have identified a variant gene that significantly increases the risk of type

2 diabetes. The work was done by deCODE Genetics, a company in Iceland that looks for genetic roots of human diseases. The gene is known as TCF7L2, and the mutation identified by researchers is very prevalent in the American population: 38% of Americans are estimated to have one copy of the variant gene (inherited from one parent) and 7% are estimated to have two copies (i.e., inherited from both parents). **The research indicates that one copy of this variant gene contributes a 45% greater risk of type 2 and that two copies confer a 141% greater risk of developing type 2.**

Background: In 2003, researchers identified a variant gene in the Icelandic population. This paper confirms the presence of the variant in both Danish and American populations. The gene controls the activity of other genes, and researchers believe that the gene may have an enteroendocrine role in the pathogenesis of type 2 diabetes. Researchers speculate that TCF7L2 may alter the levels of glucagon-like peptide (GLP-1), which works in concert with insulin to regulate blood glucose levels.

Methods: The initial Icelandic study included 1,185 individuals with type 2 diabetes and 931 unrelated population controls. The Danish cohort consisted of 228 females with type 2 diabetes and 539 controls, while the US population studied was a European-American cohort of 361 individuals with type 2 and 530 controls. Type 2 diabetes was defined as a history of fasting blood glucose greater than 126 mg/dL, two-hour postprandial glucose greater than 200 mg/dL, use of oral hypoglycemic agents, or the use of insulin and oral hypoglycemic in a subject older than age 40.

Major findings: 38% of Americans are heterozygous for the variant gene and have a 45% greater risk of type 2, while another 7% are homozygous for the variant and have a 141% greater risk of developing type 2. This corresponds to a relative risk of 1.45 and 2.41, respectively. The researchers found a 21% population-attributable risk, indicating that **21% of all cases of type 2 diabetes would disappear if this gene did not exist.** The association between type 2 diabetes and the TCF7L2 variant was highly statistically significant, with a p-value of 0.000000021 in the Icelandic population, $p=0.0048$ in the Danish cohort, and $p=0.000000003$ in the US cohort.

While the variant gene is more common in people with diabetes (32-38% of people with diabetes have the variant gene), it also is present in normal individuals (~25%). This is expected, as type 2 diabetes most likely is affected by a large number of genetic factors and is influenced as well by environmental factors.

The mutation was not characterized, nor do we know how the function of the TCF7L2 gene is altered in individuals with an association. Single nucleotide polymorphisms were identified in intron 3 of the gene, which is a non-coding region of the gene. This indicates that the problem with TCF7L2 may be the way that the RNA message is spliced together. Although introns do not encode a direct protein message, mutations in the intron region can lead to the incorrect splicing of RNA, which would then lead to non-functional proteins.

Other findings: The researchers also investigated the mode of inheritance, concluding that it fit neither the dominant nor the recessive model, as the heterozygous carriers have a risk for type 2 diabetes intermediate between that of non-carriers and homozygous individuals.

Implications: If a diagnostic test existed to identify those with the variant gene, they could be targeted to diet and exercise even *more* than the general population, because they have a higher risk of type 2 diabetes. And, it would follow, these people should be screened *much* more aggressively for pre-diabetes, since they have a higher likelihood to develop it. The discovery of mutation in the TCF7L2 gene might lead to the identification of a biochemical pathway through which diabetes develops, and could possibly be treated. Understanding more about the gene would be helpful in drug development, and future research to uncover the mechanism by which TCF7L2 relates to diabetes will be important.

—by *Erin M. Kane and Cullen Taniguchi*

8. Literature Review: JAMA reports that being overweight increases risk for CHD independently
Yan, Lijing L. et al. “Midlife Body Mass Index and Hospitalization and Mortality in Older Age.”
***JAMA*. 11 January 2006. 295 (2): 190-198.**

While there are well-established links between obesity and cardiovascular disease (CVD), this study published in *JAMA* on January 11 looks at whether the impact of obesity on CVD can be attributed solely to the association between obesity and other CVD risk factors such as diabetes and high blood pressure. In other words, is a person who is overweight or obese but has none of the other common CVD risk factors more likely to develop CVD than a similar person who is not overweight? The study looked at 17,643 individuals of varying age, sex, BMI, and cardiovascular risk levels (based on blood pressure, cholesterol, and smoking history). At the outset of the study (1967-1973) none of the participants had suffered from coronary heart disease (CHD) or diabetes. A follow-up study was conducted from 1984 to 2002 to measure the CHD-related mortality and morbidity rates of the participants in the original study.

The study found that obese participants with a low risk of CHD were 1.43x more likely to suffer fatal CHD than normal weight patients with low risk. Similarly, obese participants with moderate risk were 2.07x more likely to die from CHD than normal weight participants. Obese patients with low risk were also 4.25x more likely to be hospitalized by CHD while obese patients with moderate risk were 2.04x more likely to be hospitalized. The study concluded that obesity is a significant contributor to heart disease, independent of its association with other cardiovascular risk factors.

—by Nate S. Freese

9. Literature Review: NAVIGATOR data yield link between nonalcoholic fatty liver disease and CVD risk in type 2 patients - Targher, Giovanni et al. “Nonalcoholic Fatty Liver Disease and Risk of Future CVD Events among Type 2 Diabetic Patients.” *Diabetes*. December 2005. 54: 3541-3546.

Italian researchers report in last month's *Diabetes* that nonalcoholic fatty liver disease (NAFLD) predicts risk for CVD in patients with type 2 diabetes independently of metabolic syndrome and other classical risk factors. NAFLD is defined by the authors as “the most common abnormality observed in hepatology practice” and one that is “closely correlated to visceral obesity, dyslipidemia, insulin resistance, and type 2 diabetes.”

Fatty liver is a condition in which fat accumulates in the liver cells. A person has fatty liver disease when fat comprises at least 10% of the liver. The condition known as nonalcoholic fatty liver disease refers to fatty liver disease not related to alcoholism. NAFLD is a common condition in patients who are very overweight or who have diabetes mellitus. Indeed, the authors of the paper note that the prevalence of NAFLD was as high as 75% in their study population of type 2 diabetics.

Building on research that found that patients with NAFLD had greater carotid artery-wall thickness but did not address endpoints, the researchers tracked CVD endpoints in a population of 2,103 people with type 2 diabetes who did not show signs of CVD at the start of the study. In the five years of the study, 248 participants required angioplasty or heart bypass or suffered a nonfatal heart attack, stroke, or cardiovascular death. These subjects were matched in a 1:2 ratio with 496 control subjects of similar age and sex who did not develop CVD. Comparison of the two groups showed that, even after adjusting for age, sex, smoking history, diabetes duration, A1C, LDL, liver enzymes, and use of medications, NAFLD was significantly associated with an 84% higher likelihood of developing CVD. The study suggests that physicians detecting NAFLD in patients with type 2 diabetes should consider these patients to be at high risk for CVD. The study authors note that interventions to prevent CVD also improve NAFLD, including weight reduction and treatment with insulin-sensitizing oral antidiabetic agents.

—by Erin M. Kane

10. Dr. Steve Edelman's "Taking Care of Your Diabetes"

Taking Control of Your Diabetes (TCOYD), San Diego, CA, October 29, 2005

The 11th annual Taking Control of Your Diabetes (TCOYD) one-day conference and health fair was held in San Diego late last year. Co-directed by Dr. Leo Caballero and founder Dr. Steven Edelman, the TCOYD events are aimed at educating and motivating diabetes healthcare providers and patients. This year's session, which focused on the benefits of physical activity, drew more than 500 HCPs, patients, and family members. San Diego's Hispanic communities had a particularly strong presence at the event. The health fair featured exhibitions from Novo Nordisk, Sanofi-Aventis, Amylin, Roche, GSK, Abbott, and Becton Dickinson, showcasing new insulins, glucose meters, and pumps.

The morning session was opened by Dr. Edelman and Dr. Caballero, who welcomed the Hispanic community, reminding us just how prevalent diabetes is among America's minority groups: of the almost 21 million Americans with diabetes, 2 million are Hispanic - 24% of Mexican Americans and 26% of Puerto Ricans have the disease. Diabetic retinopathy is five to six times more common in these ethnic groups than in other patients, and Dr. Caballero stressed the need for education. Hispanics born in 2000 will have a lifetime risk of 1 in 2 for getting diabetes; Caucasians, 1 in 3.

Dr. Edelman addressed the burden of diabetes on spouses and loved ones, saying that they have "type 3 diabetes." He also introduced the concept of a "diabetes warranty program," which he described as lifestyle modification with an eye toward prevention of complications. Dr. Edelman suggested "Eight Golden Rules" for people with diabetes, listed below. If all people with diabetes followed them, the diabetes community would be much better off – if you know people with diabetes, please rip this out and send to them today!

The Eight Golden Rules:

1. Get your eyes checked once or twice a year because diabetic eye disease has no symptoms until the problems are advanced.
2. The same is true for kidney problems: there are no apparent symptoms, so have your kidney tested.
3. Buy shoes that fit and see your podiatrist.
4. Keep blood vessels clear by keeping cholesterol levels and blood pressure in healthy ranges, and make eating properly and exercise part of your everyday routine.
5. Tooth and gum disease are common diabetic problems. Brush twice a day and floss once a day.
6. Find exercise you enjoy, be it dancing, walking, or martial arts (all of which were demonstrated at the conference). It's less important what you do, as long as you do *something*.
7. Eat well-balanced meals every day. There's no such things as a 'diabetic diet.' There are no magic pills – losing weight is hard, so make small changes every day.
8. Make stress reduction a part of every day and feel empowered from knowledge. You must be the most active member of your health team.

Keynote speaker Dr. Francine Kaufman was inspiring as always and spoke about obesity's role in the growing pandemic of type 2 diabetes among children. She explained that while our genes have not changed in any significant way since Paleolithic times, our environment has changed dramatically: snack vending machines, soda, processed foods, remote controlled everything and super-size portions. Our bodies, designed for physical activity, natural food and fiber are on a "collision course" with our modern day environment. Portion sizes have actually doubled in the past 10 years. Today we consume 167 calories more/day than 20 years ago – that's an extra 17 pounds/year and most adults gain on average one pound a year. As we all know, while food consumption is up, physical activity is down. In a 45-minute

PE class, kids actually move for all of eight minutes. One in three children is considered medically obese. Those overweight by adolescence have an 80% chance of being obese adults. Thirty years ago 2% of children with diabetes had type 2 diabetes, while today it's a whopping 25%!

Dr. Kaufman's 10 Health Steps for Kids

1. Eat five fruits and veggies daily.
2. Only indulge in two hours of sedentary behavior/day.
3. Get at least one hour of physical activity daily – we were troubled to learn that in California only 20% of fifth, seventh and ninth graders can pass the L.A. fitness test.
4. Drink two to three eight-ounce glasses of water/day – sweetened drinks spike insulin production and stress the system, causing future problems.
5. Limit juice to one glass/day; eat fruit instead.
6. Drink low-fat milk. Fat in dairy is not needed after age two. (Breastfeeding seems to produce fewer overweight children and less diabetes.)
7. Avoid soda (One in four beverages consumed in the U.S. is soda.)
8. Limit fat.
9. Eat breakfast every day and eat dinner as a family.
10. Be active as a family.

Small strides are slowly being made to stem the obesity tide in children. In California a bill was passed to ban soda and junk food in schools, and diabetes specialists are trying to bring this vital information to pediatricians.

Options for later sessions included workshops covering neuropathy, healthy dining out, new therapies for Type 2, teens, pregnancy and DMV laws. DCU attended a session by Dr. Bill Polonsky, founder of the Behavioral Diabetes Institute, speaking on “Dealing with Diabetes, Stress, Depression and Other Emotional Barriers to Controlling Your Diabetes.” As many of you know, Dr. Polonsky is warm, witty and knowledgeable – patients *love* him! - and the workshop was enormously interactive. Among other lessons, Dr. Polonsky left attendees with some important coping strategies:

1. Diabetes is not, as we've been told over and over, the leading cause of adult blindness and kidney failure. *Poorly controlled* diabetes is. With good A1Cs, blood pressure and cholesterol, someone with diabetes has the same risk factors of heart disease or any other condition as someone without diabetes.
2. It's easier when you manage your expectations – realize you won't get it perfect every time but determine the range where it's good enough.
3. Employ a problem-solving coping style.
4. Decide you're in control of your diabetes, not the other way around and do what it takes.
5. Don't do diabetes alone – have someone who cares about you help you.

Dr. Polonsky also told us come January an ongoing trial to better identify low blood sugars may be looking for participants. Interested? Go to: www.bgathome.com.

Closing: New Developments: What's Here Now and What's on the Horizon for People with Diabetes.

A panel discussion hosted by Dr. Steven Edelman, Dr. Alain Baron of Amylin Pharmaceuticals; Dr. Robert Henry, MD, VA Medical Center and DiObex, and Dr. Athena Tsimikas, Whittier Institute for Diabetes. Panelists spoke on various new drugs and technologies, including some pros and cons – it was fascinating to hear the patient version of some of these therapies!

- Inhaled Insulin – Can you believe the surface area of our lungs is the size of your average tennis court? Good real estate. Thus, the insulin inhaler. This delivery system was described as a great springboard for delivery technologies and a way to make insulin more attractive to type 2s. Dr.

Henry raised the point that we're still not sure how it will affect the lungs over time – we appreciate the continued focus on safety.

- Byetta from Amylin Pharmaceuticals – Recommended for type 2s who are not in control. Byetta helps the pancreas secrete insulin by mimicking a normal compound found in the body that's released from the stomach when you eat. The other “newsy bit” about Byetta is it comes from the saliva of a poisonous lizard called the gila monster. Byetta, unlike other meds that lower blood sugar, also helps weight loss. In trials, subjects lost an average of 12 lbs. over two years. Down side? It's only available in an injection pen, but researchers are working on a once/week injection rather than the twice daily now required.
- Symlin – The first therapy for type 1s since insulin. Symlin, also from Amylin, is for type 1s and 2s. It helps control blood sugar by reducing glucose fluctuations and smoothing out the after meal spikes. Symlin reduces appetite, slows stomach emptying and suppresses glycogen breakdown by the liver. Symlin will be big news in weight loss, according to Dr. Edelman. Symlin is also available only by injection. Dr. Baron remarked, “Diabetes has long been thought of only as insulin deficiency, but we are learning it is broader than that. It's also an amylin deficiency and glycogen excess, and it's time to change our thinking about therapies.”
- Rimonabant –Developed by Sanofi-Aventis, it has been in a one year RIO- Europe study. This cannabinoid receptor inhibitor is being studied for its effect in helping people quit smoking and lose weight. Marked weight loss was observed during the first year of trial, yet it was said that people slipped in keeping the weight off the second year. Rimonabant may help prevent the onset of diabetes in the high-risk obese population.
- Omnipod – This unique insulin delivery system from Insulet started shipping last October. The product, which holds a reservoir of insulin, is the size of a quarter at its base with a rounded dome. It consists of two integrated wireless components, the pod and a Personal Diabetes Manager, a hand-held device used to program the Omnipod. The self-adhesive pod has no tubing and can be placed anywhere on the body, unlike the pump. We love the system for the freedom.
- Continuous Glucose Monitoring – The Freestyle Navigator system is exciting news – a home device for continuous glucose monitoring. It takes glucose readings every minute in real time and is minimally invasive, and a hand-held device indicates whether your blood sugar is going up or down. This could help greatly with post-meal blood sugars. Navigator is at the FDA currently, and speakers sounded very eager for approval!

Much more is coming down the pike, and the panel closed by reflecting on the importance of educating consumers. All these new drugs and products are only as good as our knowledge about how to use them.

- by Riva Greenberg

Diabetes Close Up is a newsletter highlighting notable information and events in the diabetes industry. This newsletter is put forth as an unbiased commentary on the industry and is not meant to serve as a recommendation to buy or sell (or hold!) any stocks. Companies in which Close Concerns writers have stock and/or that are current or past clients of Close Concerns include Abbott, Animas, Amylin, Johnson & Johnson, Medtronic, Roche, and Sanofi-Aventis, and a number of small, private companies. If you have any suggestions or comments regarding content, please contact info@closeconcerns.com. If you would like to subscribe to DCU, please contact subscribe@closeconcerns.com. If you would like to offer any suggestions or comments regarding content, please contact info@closeconcerns.com. More information and disclosures found on our website www.closeconcerns.com.