DIABETES CLOSE UP

Diabetes Close Up, February, 2005
No. 44
We heard, we saw, we noted/Earnings + News Roundup/Lit Review/Glucose Patent Update

T h e s h o r t e r v e r s i o n

February is a short month, but so much happened ~ and kept happening! In this issue, we review key earnings reports, news, and literature.

1. **Earnings of note ~** This earnings season itself seems like it lasted for nearly an entire quarter! Detailed commentary inside.
   - Animas: Revenue hit $20 million and profitability achieved – plus the launch of the IR 1250, an excellent new pump.
   - GSK: Avandaryl (you guessed it: Sanofi-Aventis's Amaryl +GSK's Avandia) to come by end of 2005.
   - PolyMedica Corp: PLMD (through Liberty) delivers Wilford Brimley to your TV and supplies to your door.
   - Conjuchem: The outlook is for Phase III trials for DAC: GLP-1 to start in 2006. A late February release noted that Conjuchem would present more information in DAC: GLP-1 (including, thankfully, sub-group analysis for the Metformin trial) at an April 19 analyst meeting in New York City.
   - Novo Nordisk: Levemir translated into levitation in market share and earnings for Novo's insulin franchise – Levemir already has nearly 10% of the European market, less than a year since launch. Once it reaches the US market, we believe consumers will move toward it, if for no other reason that it's said to be weight-neutral. What's a couple of pounds a year, you say? 20 pounds after ten years – and unhappy patients.
   - Johnson & Johnson: $1.7 billion in sales achieved for 2004 – LifeScan's on a serious roll again.
   - Astra Zeneca: AZ plans to file Galida (dual PPAR) in 2007; check it out, diabetes *and* metabolic disease are listed on AZ's pipeline table of indications on which they are working.
   - Bristol Myers-Squibb: Glucovance sales dropped 94% to $7 million from $109 million – power of generics.
   - Becton Dickinson: Logic monitor/strips reached $50 million in sales for the calendar year. Up next – selective international expansion for the franchise.
   - Merck: The muraglitazar filing was discussed, as were vague mentions of early stage obesity drugs.
   - Sanofi-Aventis: First billion-dollar year for Lantus – the long acting analog now accounts for 25% of U.S. insulin scripts.
   - Inamed: Most excellent DTC goings-on – the website has everything from a surgery eligibility quiz to a doc locator!
   - Aradigm: Novo now controls the clinical and commercial scale manufacturing processes.
   - Arena: Impressive deal with J&J.
2. **News of note:**
   - **DexCom Funded/Filed S-1**: DexCom announced in early January that it closed a Series D $22.5m round of funding–impressive! Blue chip private equity fund Warburg Pincus led the round; we perceive Warburg's positive nod as meaningful vis-a-vis the potential strength of DexCom specifically and of continuous glucose monitoring more broadly. In February DexCom filed to go public – find its S-1 on www.sec.gov. The company is now in a quiet period.
3. **Literature Review:**
   - **New England Journal of Medicine, *Insulin Analogues*, by Dr. Irl Hirsch, January 13, 2005**: Insulin was first discovered more than 80 years ago, and as Dr. Irl Hirsch points out in his outstanding review piece, this is considered one of the greatest medical breakthroughs of the 20th century. We can't think of

any other articles you could read on insulin that would teach you as much as this does – a great education. The piece reviews a great deal of history, particularly on improvements in this drug. Since 1921, for example, manufacturing techniques have improved significantly: 1) Early advancements involved improved production of higher quality porcine and bovine insulin; 2) in the 1930s the first long acting insulin was introduced; 3) the early 1980s saw the development of recombinant human insulin; 4) the last decade saw the launch of several analogs – Lilly's Humalog in 1996[1], Novo's Novolog in 2001, and Sanofi-Aventis' Lantus in 2001 – and we believe Novo's Detemir (not yet approved in the US) and Sanofi's Apidra (approved in the US and EU in April and October, 2004) should both be launched in the U.S. later this year. Clinical research, namely the DCCT results delivered in 1993 and UKPDS in 1998, confirmed the value of glycemic control, which then reinforced interest in insulin formulations that more closely mimic the basal and prandial components of endogenous insulin secretion. There are also still problems with insulin – optimal dosing is difficult for almost every patient I know, for example – even those who are in ostensibly good control and have A1Cs under 6.5%[2]. Writes Dr. Hirsch: "*Insulin treatment has always been as much an art as a science*" – this may partly reflect why, to this day, there is still reluctance on the part of doctors to prescribe insulin (much is made of patient resistance to insulin [weight gain, hypoglycemia, pain] but the biggest insulin resistance, it has been said, is physician resistance). Hirsch continues, "*…current insulin – replacement regimens are far from perfect; to date it is impossible to replicate normal insulin secretion. Furthermore, for some people, especially children and adolescents, a regimen of injecting insulin four times or more each day may be so challenging that at least occasional failure is inevitable. I therefore look forward to new forms of technology that will help improve insulin-replacement therapy*." This conclusion reminds us that a lot is afoot in diabetes – new forms of technology speaks, most likely, to pumps and the possibility of inhaled insulin – and we are also reminded that current research may yield other novel therapies that could take the place of or be used in combination with insulin, particularly those that are hormone based – GLP-1 and Symlin, in particular. We await them anxiously.

- **Science, January 21, 2005.** Our thoughts on this issue, which contains a great deal of focus on diabetes and obesity. See inside for Martha Nelson's take ~ 1) *How Obesity Causes Diabetes: Not a Tall Tale*; 2) *Genetic Factors in Type 2 Diabetes: The End of the Beginning?* 3) *Diabetes, Obesity, and the Brain;* 4) *Type 2 Diabetes – a Matter of Beta Cell Life and Death?* 5) *Mitochondrial Dysfunction and Type 2 Diabetes.*
- **JAMA, February 10, 2005, *Single-Donor, Marginal-Dose Islet Transplantation in Patients with Type 1 Diabetes*, by Bernard Hering, *et al*.** We rant inside about how the *New York Times* covers pieces like this irresponsibly.

4. **BMY Analyst Day**: Muraglitazar musings were the word of the day – our "cut-through-the-non-diabetes-clutter" overview of last November's analyst R&D meeting.
5. **New column-Glucose Patent Update:** *Beginning with this issue of Diabetes Close Up, we will publish a periodic update of emerging intellectual property in the area of glucose monitoring. This survey will cover recent patents and applications in U.S., Europe, and world publications. A table will be provided listing all citations and statistics will be presented listing the number of citations in broad categories. In addition, several citations will be selected for a brief review and description. These updates are compiled and edited by D. Bommi Bommannan, PhD, JD, and Russell Potts, PhD.*
6. **Errata & etc.** New section!

[1] Noted Dr. Hirsch recently, "*Lispro came to us on August 6, 1996. I'll never forget the date – my patients were lined up to the elevator waiting for the first samples*."

[2] We say ostensibly because an A1C of 6.5% doesn't always translate into perfect insulin dosing or perfect control – in fact, it may actually reflect significant bouts of hypoglycemia followed by carbohydrate (over)correction, followed by hyperglycemia, followed by insulin (over)correction – an overcorrection vortex, basically.

T h e l o n g e r v e r s i o n

1. Fourth Quarter, 2004 Earnings of Note

Animas

- Fourth quarter 2004 net revenues of $20.0m represent 82% growth over adjusted net revenues for Q4'03.
- Improved gross margin of 60% compared to an adjusted gross margin of 51% in the prior year's fourth quarter.
- SG&A expenses as a percent of adjusted net revenues fell to 49%, compared to 64% in Q4'03.
- For the first time in the company's history Animas recorded a profit on an adjusted net income basis: $0.5m in the fourth quarter, compared to an adjusted net loss of $2.7m in Q4'03.
- For the first quarter of 2005, the Company anticipates net revenues between $17 and $18m, compared to the first quarter of 2004's adjusted net revenues of $9.3m, an increase of approximately 90%. The insulin pump business is seasonal, with first quarter revenues typically lower than the preceding fourth quarter revenues as a result of patients' having met their insurance deductibles.
- According to Crothall, the Animas IR 1250 will be the "coolest," smallest, most technologically advanced pump on the market. It comes in three metallic colors and plays music tunes for alerts (important to teen patients). The new model will be more user-friendly, precise, and durable than past models. The IR 1250 is smaller, lighter, and thinner than other pumps on the market; its "coolness" is clearly a major selling point with the company. The model will also have an improved user interface, plus a new CalorieKing-derived food database with capacity of 500 food items. Going forward, Animas plans on new product launches every six to nine months.
- Animas remains focused on type 1 diabetes patients and type 2 patients requiring insulin therapy. Less than 25% of type 1 patients in the U.S. are on insulin pumps and in Europe the figure is not quite 7%. According to Animas, this worldwide market, worth $780m today, is growing at 20% per year. Animas has room to grow – today Animas holds 13% of the U.S. pump market
- Animas recently signed an exclusive licensing deal for micro-pump technology with the Swiss company Debiotech, S.A. They anticipate launching the market's first micro-pump in 2007. Animas expects the device to be *one-quarter* the size of the IR 1200 pump platform, with greater dosing precision and accuracy. Animas also acquired micro-needle technology from Debiotech but has not announced a date for a first product release.
- In December, Animas signed an agreement to purchase the assets of Cygnus, including its IP in glucose sensing. Animas hopes to develop a sensor 1000x more sensitive than blood glucose testing strips. They hope to combine the micro-needle with the electrochemical sensor of the GlucoWatch, Cygnus's flagship product. Crothall stressed that Animas has a strong IP position for present and future products. (A detailed account of these acquisitions is provided in our summary of Animas' presentation at the Piper Jaffray conference held in January.)
- On the financial front, 2005 revenues are projected in the $82-84m range. SG&A, which has improved thanks to increased sales rep productivity, is expected fall even further in the next year. Gross margins will continue to increase (to a projected 70% in 2007) because of better absorption of overhead costs and falling costs of disposable products.

GSK

- Diabetes drugs up 32% for the full year (Avandia/Avandamet). Hopes to launch Avandaryl (you guessed it: Sanofi-Aventis's Amaryl + GSK's Avandia) by end of 2005.
- DPP-IV inhibitor showed significant efficacy in reducing plasma glucose levels over 24hr period – hoping for 1x-day dosing. Anticipating Phase III trials in 2006.
- Avandamet #1 in its class
- Definitely optimistic on its diabetes platform, but it's a small part of a very large business.
- The obesity compound called "771" has been abandoned due to insufficient efficacy.

PolyMedica Corp makes its money in diabetes by doing business as Liberty Medical – you've seen those ads featuring Wilford Brimley, the old Quaker Oats guy. Some highlights from PLMD's 3Q '04 earnings call

- For 3Q '04, PolyMedica reported income of $78.7m for its Liberty Medical segment, representing a 14.2% increase over the same quarter of 2003. Pre-tax margin was 17.6% compared to last year's 16.6%.
    - Total company revenues for the quarter, inclusive of PolyMedica's Liberty Healthcare division (focused on chronic obstructive pulmonary disease) and pharmaceutical sales, were just over $114m.
- With 674,000 active diabetes patients in 2004, Liberty's patient base was up 12% versus last year.
- In less happy news, this March will be first month in which Liberty must contend with new reimbursement from Medicare, including a 3% cut in reimbursement for diabetes supplies.
    - Steeling itself for this blow, PolyMedica engaged consultants to gauge improvement in customers' lives – they want to demonstrate that their customers are healthier because of their service.
- Returning to the positive: PolyMedica acquired National Diabetic Assistance Corp. in February 2005 for $17.1m total ($13.6m for assets and patient list + $3.5m for Deerfield Beach, FL, real estate).NDAC was probably a wise buy for PolyMedica, having reported $15m in revenue in 2004 from 29,000 customers.
    - PolyMedica management said that the cost of the acquisition compares favorably to acquiring new patients via TV ads (Wilford Brimley must not come cheap these days…or maybe it's just that daytime TV ads are getting more expensive).
- Looking to the future, PolyMedica expects continued growth for Liberty Medical – and is preparing to enter the commercial insurance marketplace to realize it.
    - Especially considering the impending 3% cut in Medicare reimbursement, Liberty cannot afford not to capitalize on the opportunity presented in the 200 calls per day that it claims to receive from non-Medicare diabetes patients.
- We'll keep watching this: our crystal ball tells us that sales revenues for diabetes products will become ever-more dependent on mail-order pharmacy distribution channels in the next several years. Mark our words!

Conjuchem

- Conjuchem will present data from both the Phase 1 (modified diluent) and Phase 2 (metformin) trials of DAC: GLP-1 on April 19 in New York City. Thankfully, sub-group analysis would be presented. Regarding the latter, in its earnings release (Conjuchem doesn't do earnings calls), the company said that DAC™: GLP-1 Phase II results demonstrated a ~1% decrease in blood glucose levels, while normalizing 58% of the patients in the optimum dose group. These are always tough results to interpret – so many questions: How did the placebo group perform? What were baseline A1Cs? How did the side effect profile, especially nausea, look across the groups?
- Re: the quarter, there wasn't so much of note. Net research and development expenses totaled ~$38m for the year ended October 31, 2004, compared with $23m for the year ended October 31, 2003. The increase was said to be largely attributable to costs relating to the DAC™: GLP-1 clinical trial program as well as other trials.
- G&A rose $1.7m to $5.0m – interestingly, part of the increase was attributed to an "aggressive" investor relations program in the United States and Canada.
- At October 31, 2004, the Company had cash and cash equivalents of ~$27m and a working capital position of ~$22m. The Company says it is currently pursuing a number of initiatives to raise additional capital. We are curious about partners. ConjuChem noted that its ability to continue its planned level of clinical development and to continue to operate at our planned activity levels required additional funds.
- Outlook: Part of its "aggressive clinical trial agenda" for 2005 will include work that will allow Phase 3 trials for DAC: GLP-1 to start in 2006.

Novo Nordisk

- For 2004, total diabetes revenue was DKK 20.533bn–up 11% reported, 15% in local currency. Novo's diabetes segment also grew 11% in the fourth quarter.
- Insulin analogs represented DKK 4.507bn, up 77% reported, 84% local currency.
- Novolog and NovoMix both grew well. For the quarter, analogs reached DKK 1.332bn, up 68%.

- Novo has seen 60% growth in the U.S. market for its insulin analogs. Prices have gone up around 5% on analogs and human insulin in U.S. In response to questioning, management noted that volume growth in insulin was 4.5% worldwide, 2% in the U.S.
- Human insulin sales: Novo reported DKK 14.383bn down 1% reported, up 2% local. For the quarter, this segment was flat.
- Oral medications were up 15% reported, 21% local, at DKK 1.643bn. For the quarter, orals were up 4% at DKK 0.403bn
- Novo says it has 50% of the worldwide insulin market and 30% of the worldwide insulin analog market.
- Levemir is now available in a pre-filled cartridge for use in insulin injection pens – one possible factor in its success in Europe, where insulin injection pens are the norm. (Recall that Aventis suffered somewhat in reputation if not necessarily in market penetration when it initially released Lantus in the EU with an injection pen some patients found hard to use and/or uncomfortable.)
- Levemir, introduced around Europe in 2004, now accounts for 9% of the European long-acting analog market. We'll be looking for U.S. approval in mid-2005, once the FDA is satisfied with Levemir's efficacy across ethnic groups.
- Management said Novo is stripping share away from Lilly. Insulin share battles are becoming more interesting – obviously as Levemir begins to gather speed, Sanofi-Aventis will likely lose some long-acting analog strength, although Sanofi-Aventis may make up for it with its new rapid-acting analog Apidra (glulisine).
- 4.5% volume growth; 2% volume growth in the U.S.
- In November 2004 Novo broke ground for a new Levemir production facility in Kalundborg, Denmark.
- As reminders: 1) Liraglutide is in Phase 2b trials – Phase 3 trials were delayed as reported last quarter and should start toward the end of 2005 or early 2006. 2) Novo now has full manufacturing rights for Aradigm – we await further information on progress in this area.

Johnson & Johnson

- For 2004, LifeScan's global sales hit $1.7bn, up a very strong 19% (15% excluding foreign currency effect). U.S. sales for 2004 hit $920m, up 13%, and international sales reached $781m, up 28% (18% excluding FX).
- For the fourth quarter, global sales reached $461m, up 19% (15% excluding FX effect). U.S. sales rose to $240m, up 12%, and international sales reached $221m, up 28% (20% excluding currency gains).
- Notably, $240m represents a quarterly record for U.S. sales for LifeScan. Annualizing nearly $1bn in domestic sales alone is impressive, particularly since we are thinking growth likely came more in volume than in price.
- The $221m of international sales is also a record and in fact the highest international sales figure recorded prior to this was $195m, last quarter – clearly international is also on a roll.
- It should be noted that the U.S. growth comparison is an easy one since growth in the fourth quarter of 2003 was just 1%. By contract, the international comparison stood up well, since international growth in the fourth quarter of 2003 was a robust 29%. How much international growth represents product diversion remains a question, although clearly growth is no longer coming at the expense of domestic growth.
- In addition to pricing, we are also interested in channel and how it is changing in terms of mail order, etc. No information on this was given on the call.
- Nothing on the dual-PPAR agonist, although we assume JNJ is working on rodent studies.

Astra Zeneca

- Galida, AZ's dual-PPAR agonist, is still in Phase 3 – it needs to complete this additional rodent safety study (cancer concerns) and plans to file in 2007. Intriguingly, AZ is listing this compound as under study for diabetes *and* metabolic syndrome on its pipeline table. Now if we think 12m diagnosed type 2 patients (in the U.S.) represents a big number, how about 41m with pre-diabetes?
- AZD6610, a Phase 1 compound, is in early study for dyslipidemia (AZ is studying seven [four preclinical and three Phase 1] compounds for this indication) and diabetes. Anticipated filing is "beyond 2007." AZD8677, also under study for dyslipidemia/diabetes, is a preclinical compound.

- AZ is looking at Atacand (candesartan cilexetil) for diabetic retinopathy – the compound, currently marketed for high blood pressure, is in Phase 3 retinopathy studies, but AZ expects to file it after 2007.

Bristol Myers-Squibb

- Glucovance got absolutely destroyed: $7m in overall sales – down 94% from 109m For full-year, $169m sales WW ($165m US) – down from $424m/$419m a year ago.
- Nothing new on muraglitizar.
- BMY has style: they played "Oye Como Va" by Santana for the pre-call Muzak.

Becton-Dickinson

- Diabetes care revenues rose 19% versus a year ago. In the U.S., diabetes care revenues rose 18%. International sales increased 21% (7% excluding the impact of foreign exchange).
- Diabetes sales were stronger in 1Q '05 than expected. Since this business is relatively higher margin (high 60s to low 70s percentage range) this boosted the margin slightly. Strength was attributable to various sources, including:
    - Strong pen needle sales in Japan and Europe (where BD recently went to direct distribution in several countries). Management believes this pen needle strength is likely sustainable.
    - Blood Glucose Monitoring strength: Blood glucose monitoring sales came in at $15m, similar to last quarter (up $4.0m from two quarters ago). Management indicated that its focus is North America (approximately 50% of WW spending is in the U.S.). However, they are looking internationally and anticipate that the end of this year could see international launches. Decisions will be made on a country-by-country basis; we should not expect to see continent-wide entry into the blood glucose monitoring market.
- Management stated that they do not expect diabetes revenues to continue to grow at such a strong rate all year. They predict that Q2 is likely to be the weakest quarter for this business.

Merck

- **Merck had almost nothing on diabetes on its call**. They mentioned that muraglitazar is filed and that they're excited about it, but no real information was given. Consistent with a trend in Big Pharma, they mentioned that they are working on obesity drugs, but gave no details.

Sanofi-Aventis

- Lantus sales 2004: 843m Euros worldwide, up 80%. U.S. sales of 495m Euros (an increase of 57%), while 295m Euros in international sales (increase of 111%). Notably, it actually did take four years for the drug to reach over $1.0 billion in sales.
- Lantus now accounts for 24.5% of total insulin prescriptions in the U.S. In the fourth quarter, Lantus sales reached 219m Euros worldwide, with 131 Euros flowing from the U.S. (up 36%), and 88m Euros overseas, (up 63%).
- Amaryl sales rose 19% worldwide to 684m Euros for the year. U.S. sales of 216m Euros represented an increase of 32% while international sales rose 9% to 239m Euros. In the fourth quarter, Amaryl worldwide sales reached 128m Euros, with U.S. sales of 62m, up 42%, and international sales of 66m euros, up 8%. We believe Amaryl sales will start to suffer as generic competition enters and as the Lantus "one shot a day, one pill a day" campaign slows. This campaign has been strong from the start as we understand it, as sales reps have pushed the "simple" therapy message – however, once Apidra is launched and there is a rapid-acting insulin to sell, marketing messages will need to change at least a bit! As we believe many more patients *should* be on prandial insulin than *are*, particularly Lantus users, we look very forward to the launch of Apidra, from a system perspective. In addition to the Apidra launch, Levemir will soon be competing for the same patients, and particularly if the weight benefit is seen in many patients, this insulin could be a strong competitor.
- Regarding Acomplia and whether it will be fast-tracked, management responded that it would be "delighted" if the product were fast-tracked but it does not have any word from the FDA on this front.
- No new news on Exubera.

Inamed

- Obesity sales rose 47% to $26m. For the full year, obesity sales reached $89m, up 40%. Stellar result!

- The company appears to be focused on developing key targeted accounts, which should drive volume.
- This quarter, they launched DTC marketing for LAP-Band, featuring success stories, a quiz to determine surgery eligibility, and a physician locator service. The website, http://www.lap-band.com, is slick and ever-so user-friendly.
- The company will file request-for-coverage with CMS for fuller national coverage of LAP-Band.
- Management looks for sales to grow at least 30% in 2005, which sounds conservative to us, even from this higher base.
- Happily, the company is still looking to improve every aspect of LAP-Band. It noted that the LAP-Band is a very different product today compared to what it was at its 2001 launch, featuring at least seven major improvements versus the initial product.

Aradigm

- In January Aradigm and Novo Nordisk (and its new subsidiary Novo Nordisk Delivery Technologies) announced the successful closure of their restructured license agreement. We will be eager to see how movement evolves on development and the commercialization of the AERx insulin delivery system.
- The licensing agreement maintains Aradigm's long-term financial interest in the product through a royalty on worldwide sales of the system.
- Apparently the CEO of Novo Nordisk recently made public comments causing some analysts to question Novo's commitment to the AERx program. When asked about these comments and Novo's attitude, Aradigm management indicated that they have observed no substantial change in Novo's goals for or prioritization of the program.
- During Q&A on the conference call one analyst asked about an FDA requirement that the product be approved for use in both type 1 and type 2 diabetes. In response, management explained that before it can be approved the product has to be demonstrated to be safe in all patient groups who might have access to it: both type 1 and type 2 patients.
- Also during Q&A on the conference call an analyst asked about prospects for AERx reimbursement in Europe. Management avoided answering this question by responding that there is no one who knows more than Novo Nordisk about the complicated reimbursement process.

Arena

- In the fourth quarter, APD356, an internally discovered product candidate for the treatment of obesity, was advanced into clinical trials. A randomized, double-blinded, multi-dose, 28-day Phase 2 study in approximately 400 obese subjects was initiated.
- Pending positive results, the next step would be an advanced Phase 2 study lasting three months (with roughly the same number of patients). After that, Arena would pursue a study of one year in length.
- Arena is currently conducting three-month and 12-month toxicology studies in animals. Management expects to complete these studies relatively soon, paving the way for a three-month human study.
- Along the way, Arena hopes to find a partner who would assume responsibility for these clinical trials.
- During 4Q, Arena established a world-wide collaboration with Johnson and Johnson's Ortho-McNeil for its pre-clinical diabetes program, 19AJ. Arena received an upfront payment of $17.5m in January 2005. Arena has already achieved two preclinical development milestones totaling $5.0m in the Ortho-McNeil collaboration. This deal strikes us as a pretty large deal considering it's all preclinical, and we look forward to watching progress on the two compounds, both of which target a unique GPCR target on pancreatic beta cells.
- The program's goal is to help patients with type 2 diabetes control blood glucose levels without risks of hypoglycemia by stimulating insulin secreting cells of the pancreas. Compounds would be delivered as oral medication. Management described this as a potential new *first-line* therapy – again, we'll be eager to see some data.
- Going forward, Arena is eligible for up to $600m in milestone payments and double-digit royalties based on sales.

–by Sara S. Dauber, Melissa P. Ford, Stephen D. Simpson and Kelly L. Close

2. News of Note –DexCom Funded, Files S-1

***DexCom Closes Round, Files S-1*:** San Diego-based continuous monitoring company DexCom announced in early January that it closed a Series D $22.5m round of funding. Impressive! Blue chip private equity fund Warburg Pincus led the round and Sean Carney, a managing director there, has joined DexCom's board of directors. This investment represents Warburg's first investment in a diabetes company, and we perceive Warburg's positive nod as meaningful in terms of the potential strength of DexCom specifically and of continuous monitoring more broadly. Warburg has invested in healthcare since 1971 and has invested $1.1bn in the medical device industry, including standout investments Kyphon, American Medical Systems, and Wright Medical. Earlier this month, DexCom filed to go public, so is now in a quiet period – see its S-1 on www.sec.gov.

We remain very enthusiastic about the prospects for continuous monitoring and believe that both external and implantable monitors will prove to be large market segments. Sometimes people ask us how so many firms can possibly survive – we think the emergence of continuous will ultimately expand the blood glucose market meaningfully. Right now, even if we test a dozen times a day, we still have no idea of direction or rate of change – we can't wait for the day that continuous monitors can provide such information. Glycemic variance will have the potential to be reduced significantly – and when you get right down to it, we've been waiting for a tool that can really help in this regard since DCCT made it so plainly evident the importance of lowering A1C in order to reduce complications. Yes, traditional monitors have improved, significantly so, but this improvement – what a leap forward it will be for all patients, families, and healthcare providers. Onward, continuous manufacturers! This is worth waiting for.

–by Kelly L. Close

3. Literature Review

New England Journal of Medicine, *Insulin Analogues*, by Dr. Irl Hirsch, January 13, 2005: **Insulin was first discovered more than 80 years ago, and as Dr. Irl Hirsch points out in his outstanding review piece, this is considered one of the greatest medical breakthroughs of the 20th century.** We can't think of any other articles you could read on insulin that would teach you as much as this does – a great education. The piece reviews a great deal of history, particularly on improvements in this drug. Since 1921, for example, manufacturing techniques have improved significantly: 1) Early advancements involved improved production of higher quality porcine and bovine insulin; 2) in the 1930s the first long acting insulin was introduced; 3) the early 1980s saw the development of recombinant human insulin; 4) the last decade saw the launch of several analogs – Lilly's Humalog in 1996[3], Novo's Novolog in 2001, and Sanofi-Aventis' Lantus in 2001 – and we believe Novo's Detemir (not yet approved in the US) and Sanofi's Apidra (approved in the US and EU in April and October, 2004) should both be launched in the U.S. later this year. Clinical research, namely the DCCT results delivered in 1993 and UKPDS in 1998, confirmed the value of glycemic control, which then reinforced interest in insulin formulations that more closely mimic the basal and prandial components of endogenous insulin secretion. There are also still problems with insulin – optimal dosing is difficult for almost every patient I know, for example – even those who are in ostensibly good control and have A1Cs under 6.5%[4]. Writes Dr. Hirsch: "*Insulin treatment has always been as much an art as a science*" – this may partly reflect why, to this day, there is still reluctance on the part of doctors to prescribe insulin (much is made of patient resistance to insulin [weight gain, hypoglycemia, pain] but the biggest insulin resistance, it has been said, is physician resistance). Hirsch continues, "*…current insulin – replacement regimens are far from perfect; to date it is impossible to replicate normal insulin secretion. Furthermore, for some people, especially children and adolescents, a regimen of injecting insulin four times or more each day may be so challenging that at least occasional failure is inevitable. I therefore look forward to new forms of technology that will help improve insulin-replacement therapy*." This conclusion reminds us that a lot is afoot in diabetes – new forms of technology speaks, most likely, to pumps and the possibility of inhaled insulin – and we are also reminded that current research may also yield other novel therapies that could take the place of or be used in combination with insulin, particularly those that are hormone based – GLP-1 and Symlin, in particular. We await them anxiously.

–by Kelly L. Close

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[4] We say ostensibly because an A1c of 6.5% doesn't always translate into perfect insulin dosing or perfect control – in fact, it may actually reflect significant bouts of hypoglycemia followed by carbohydrate (over)correction, followed by hyperglycemia, followed by insulin (over)correction – an overcorrection vortex, basically.

Science, January 21, 2005

In our view, the January 21, 2005 issue of *Science* magazine deserves special attention from many of our readers: it devotes a special section to type 2 diabetes and investigates several key pathways involved in this complex disorder. Five feature articles describe a range of biological agents implicated in the development of type 2 diabetes. First, "Genetic factors in type 2 diabetes: the end of the beginning?" provides an overview of current knowledge regarding the contribution of genetic susceptibilities to type 2 diabetes in general, as well as several specific genetic polymorphisms. Second, "How obesity causes diabetes: not a tall tale" considers the link between obesity and diabetes from the perspective of evolutionary theory. Third, "Diabetes, obesity, and the brain" follows up on the observations of Claude Bernard over a century ago that the brain plays a critical role in regulating body fat and glucose metabolism. Penultimately, "Type 2 diabetes – a matter of β-cell life or death?" focuses on the role of β-cell dysfunction in type 2 diabetes. Finally, "Mitochondrial dysfunction and type 2 diabetes" discusses the role of mitochondrial defect in insulin resistance, β-cell dysfunction, and, ultimately, type 2 diabetes. The issue also contains an editorial on the spread of chronic disease worldwide, particularly in India and Asia. Thus, this special feature anticipates the future of diabetes research and lays groundwork for its expansion into the fields of genetics, neurology, evolution, and healthcare in developing countries.

The opening editorial of this diabetes feature issue compares the search for the biological underpinnings of diabetes to a crime scene investigation. As demonstrated by the wide range of scientific studies presented and the multiple biological pathways potentially implicated in diabetes they describe, the trail of evidence for the cause of diabetes has led researchers to look far beyond pancreatic β-cells, to consider the roles of many other organs implicated in glucose homeostasis, including muscular, adipose, and even brain tissue. However, while these studies focus on different biological pathways – from mitochondria to brain signaling to the evolution of genes – common threads link these pathways to insulin resistance and to abnormal glucose metabolism.

Throughout these studies, the importance of genetics in the study of diabetes is emphasized: genes themselves constitute only one risk factor for diabetes, and environmental factors are crucial as well. Yet genetic research provides a powerful tool for identifying defects in the metabolic pathway that lead to diabetes and potential therapeutic targets. Pharmaceutical therapies could be targeted to different diabetic subgroups sharing specific genetic abnormalities (pharmacogenetics). For example, patients with mature onset diabetes of the young (MODY) resulting from HNF1α mutations respond particularly well to treatment with sulfonylureas, which stimulate insulin release from β-cells. The fruitless search for a single genetic cause of diabetes has improved our appreciation of the complexity and heterogeneity of diabetes and the range of disorders that can contribute to hyperglycemia.

Animal models offer the most efficient ways to conduct genetic studies, as researchers can knock out genes in murine models and then observe phenotypic effects in the animal. However, animal models may not be completely reliable models for the study of diabetes. Animal pathways for the development of diabetes may not be as similar to human mechanisms. Many examples of mutated genes known to cause diabetes in humans have no effect in animals – and vice-versa. Though much diabetic research relies heavily upon animal studies – including the research described elsewhere in this issue of *Science* – researchers must learn how best to utilize animal models and how to extrapolate information from animal studies most appropriately.

Rather than separating genetic and environmental causes of diabetes, researchers are trying to generate an integrated understanding of how our genes and environment interact to trigger diabetes onset. One example of this synthesis involves the application of evolutionary theory to diabetes: forces of natural selection could actually favor genes that cause obesity and disease if they confer other advantages, such as storing energy efficiently during times of starvation, particularly during fetal development in the womb. Natural selection may also have historically favored genes that shift glucose quickly from muscles to the inflammatory cells in order to stimulate the immune response needed to ward off infection. Thus, the very genes that put us at risk for obesity and diabetes in the long term may have been selected in the past because they may offer immediate advantages. Thus, an evolutionary approach to diabetic research may illuminate the complex interactions among genes, obesity, and diabetes.

Another emerging field of diabetic research involves the brain and neurology. The brain is actually sensitive to insulin, relying on signals from insulin, leptin, and nutrients to regulate body fat content and hepatic insulin sensitivity. Reduced insulin delivery to the brain causes weight gain and hepatic insulin resistance. Because a single signal transduction mediates the neuronal actions of both insulin and leptin, defects in this biochemical

pathway can potentially cause resistance to both insulin and leptin. Thus, the neuronal theory provides a potentially unifying theory for obesity's contribution to both insulin and leptin resistance.

Although β-cells have long been implicated in both type 1 and type 2 diabetes, much remains to be understood about why β-cell mass decreases in type 2 diabetics when β- cells normally efficiently compensate for increased metabolic load, obesity, and insulin resistance via increased replication and neogenesis.

The need for further diabetic research and new therapeutic targets is emphasized in an editorial on the spread of chronic disease worldwide. The world is recognizing that chronic disease is not restricted to wealthy Western societies, but is rather a global burden. International leaders are finally taking action, as demonstrated by the World Health Organization's Global Strategy on Diet, Physical Activity, and Nutrition in 2004 (which the U.S., of course refused to endorse). However, while the similar 2003 Framework Convention on Tobacco Control (FCTC) carries the force of international law and has stimulated worldwide increases in tobacco excise taxes, marketing bans, and smoke-free areas, best-practice solutions to obesity have not been established, undermining the real policy impact of the Global Strategy. A recent report by the World Health Organization on Priority Medicines for Europe and the World (11/2004) emphasizes the need to expand global access to drugs that address chronic diseases and their sources, including statins, antihypertensives, aspirin, and smoking cessation products, as well as further investment to develop a heat-stable insulin. Thus, future directions in diabetic research must consider the nature of diabetes in different societies. Researchers and policy-makers must devise interventions effective in non-Western cultures and among non-Western peoples in addition to improving diabetes interventions in the West.

The universe of diabetes research has expanded significantly in recent years. While the expansion of diabetic research across several scientific fields represents increased appreciation for the complexity of the disease and offers a new range of targets for therapeutic interventions, unifying these diverse fields poses its own challenges. This *Science* issue made no attempt to combine these different lines of research into a more coherent single picture of the future of diabetes research; in truth that task must fall to researchers.

–by Martha I. Nelson and Melissa P. Ford

Editorial
On *JAMA*, "Single-Donor, Marginal-Dose Islet Transplantation in Patients with Type 1 Diabetes" (February 16, 2005) and the *New York Times's* Reporting Thereof

This piece in *JAMA* – yes, the *Journal of the American Medical Association*! – reported that islet transplant clinician-researchers using a particular protocol found it possible to do transplantations in eight patients using one cadaver's pancreas per recipient, rather than the current standard of two or more pancreata per patient. The next-day, the following headline/sub-headline appeared the *New York Times*: "Progress Seen In Transplants for Diabetes – Doctors may have found a way around a major obstacle in the effort to perfect islet-cell transplants …" I read this on my BlackBerry at 3 a.m., while my husband John was away on business. I hadn't clicked through to the article yet but rang him immediately: "*Johnny*!" I said. "OMG, I'm so excited. There's what sounds like a major piece in JAMA – they only do major pieces, you know – there has been major progress in islet cell transplantation! They must have figured out a cell source! OR, they have figured out the immunosuppression nightmare. Or maybe everyone is remaining insulin independent! One of those major problems must've been solved!" Said John, groggily but happily, "Excellent, ring me back immediately when you find out – I'm going back to sleep!" As it happened, our server was down, so I couldn't click through – oh, the agony! I waited an hour, the server came up, and I clicked through to the *New York Times* story with bated breath.

The first sentence in the *NYT* piece: "Doctors may have found a way around a major obstacle in the effort to perfect transplants of islet cells, an experimental treatment for Type 1 diabetes, a severe form that often begins in childhood." "*Okay, good; sounds promising so far*," I thought. Tangent/sidebar: I'm often annoyed when type 1 is referred to as the "more severe form." Really, they're such different diseases and both can be managed optimally and mismanaged terribly. If anything, perhaps type 2 should be labeled the more severe, because more factors are difficult for patients to control: insulin resistance, lipids, hypertension, weight…plus type 2 is more progressive, which isn't great given the often delayed diagnoses.

The *NYT* Article continued: "Such transplants usually succeed only if islet cells from the pancreases [*sic*] of two or even three donors are used – a significant drawback, given the scarcity of donor organs. But now, in a trial of eight patients …doctors have managed successful transplants of islet cells … with the pancreases [*sic*] of single donors." So absolutely, this is positive. This progress occurred as a result of some excellent research on the effects of anti-inflammatory drugs, which seem to permit more transplanted cells to endure. Too, they cultured the cells for a longer period which apparently also helped, although it is unclear why. This is positive all right, because people with severe hypoglycemic unawareness absolutely benefit from the transplantations, and the more efficient the better. Unfortunately, due to a number of reasons, although there should be 6,000 cadavers per year from which islet cells could be drawn, the real number is probably closer to a tenth of that.

Last sentence of the *JAMA* conclusion: "*These findings may have implications for the ongoing transition of islet transplantation from clinical investigator to routine clinical care*." Routine clinical care. Let's think about this. This finding is very, very positive, no arguments. But is it really deserving of such conclusions that prompt widespread misunderstanding among the public? One implication of this piece is that islet cell transplants will soon be routine. Is that right? No, *not even close*, it doesn't seem.

I should say, before I get into trouble, that I take more exception to the *New York Times*, particularly since more patients and PCPs will see that and get needlessly excited. My husband John said dejectedly when we spoke in the morning, "Why didn't you call me back? Does this mean you won't be able to call Dr. Masarani and Gloria and ask them how we sign up for an islet cell transplant?" And John knows what an islet cell transplant means – that it doesn't guarantee insulin independence indefinitely, that the necessary immunosuppressant drugs have bad side effects, that at some point a choice between returning to diabetes and meeting one's maker may need to be made, that it all may be pointless to think about because the supply problems are so pervasive.

But so let's play it out anyway. There are fewer than 6,000 cadavers per year in the U.S. Let's pretend that that means that you could get 6,000 pancreata. This wouldn't be possible for a variety of reasons: often the pancreata are allocated to pancreatitis patients first and leftover pancreata aren't in good enough shape for the harsh islet isolation process, other organs are harvested first and a pancreas wilts, etc. But pretend that you could get 6,000 pancreata and as a result of this (n=8) experimental protocol, we find that this may mean there could be 6,000 patients per year that could receive transplants, rather than 3,000 or 2,000 or even 1,500, seeing as currently islet cell transplantations usually require 2-4 pancreata. But – and I have all the respect in the world for the authors, BUT – with there being (conservatively speaking) 1,200,000 type 1 diabetes patients in the US, is moving from 3,000 potential candidates for transplantation to 6,000 really meaningful in terms of routine clinical care? Given the other problems, this reducing the number of pancreata needed per transplant does not solve the problem of too few islet cells for too many type 1 patients and our problem is that headlines implied that perhaps it would.

Even if 3,000 transplants are better than 6000 – 0.3% of U.S. type 1 patients compared to 0.5% of U.S. type 1 patients – should type 1 patients be eager to receive islet cell transplants given the current environment? Well for now, I would say *no*, not unless they suffer from severe hypoglycemic unawareness or any number of *bad*, bad complications. Right now, forgetting the supply problem, the immunosuppressive regimens required post-transplant are still daunting. Perhaps not so daunting for those with hypoglycemic unawareness but daunting for patients in good control. . Tough drugs are still required – Tacrolimus and Sirolimus, to name two of the usual suspects. And let's say that we *fixed* the drug problem (which we surely hope will happen)? Even then, the supply issue looms – there is still no good cell source, so we're back to small, as in very small, numbers of patients that might benefit. And say that we fix *that* problem? Well, a depressingly low percentage of islet cell recipients are insulin-independent two or three or five years out – 82, 50, and 15 percent, respectively. Well, you might say, at least they have to take one-third to one-half of the insulin they needed pre- transplant! But, as they say, *insulin is not a cure*.

–by Kelly L. Close

And speaking of insulin not being a cure. Children With Diabetes has done a very impressive job with bracelets that say just that – see www.childrenwithdiabetes.com. The bracelets are $5 each and I bet if you send one or more to patients with diabetes that you love, they'll be delighted. I look at mine every day and remember what it is that all the good basic researchers are trying to do. Jeff Hitchcock, who heads Children With Diabetes, an incredible support organization for children who have diabetes and their families, tells us that the bracelet came from a discussion among the CWD international diabetes youth association group -- the teens. They wanted to do something special to raise money to support their causes, and they decided on the bracelet. It's been a huge success,

to the point that CWD has been able to donate over $30,000 to charity to date – they've sold 18,700 so far. The company that makes the CWD "Insulin is not a cure" bracelet is the same company that makes the yellow Lance Armstrong "LiveStrong" bracelet. In that case, 20 million bracelets were purchased by Nike, who donated them to the Lance Armstrong Foundation. CWD doesn't have the budget of Nike - that's why Nike can "sell" them for $1 -- every penny is a donation. CWD has to buy theirs - the initial batch cost more than $2 each due to mold costs. With $2 from each going to charity, the remaining $1 barely covered the cost of processing and shipping orders.
For a while, Laura Billetdeaux, who helps run CWD, was processing 75 separate orders a day, which is a lot for one person to do. That's a good problem to have. When we spoke to her earlier today, 15,000 bracelets had just been deposited in her dining room and another 5,000 were on the way. Said Laura: "*I'd love to be able to see the table again... which will only happen when we've sold all those bracelets and donated another $40,000 to research …*" Please consider ordering one today for those in your life that have diabetes.

–by Kelly L. Close

4. BMY Analyst Day, 2004

Better late than never! On November 17th, 2004, Bristol Myers-Squibb presented its annual research and development review. We had such good feedback on the Lilly R&D day that we wrote about in December that we've decided we'll try to cover all of the major R&D days for you, attempting, as always, to cut through the clutter and give you the *just* diabetes/obesity/metabolic disease update ("*It was so nice not to have to sit through comments on Prozac*," sighed one reader electronically. Well, good! We aim to please.) Some highlights from BMY's diabetes pipeline and notes on LEA29Y, the islet-cell-transplantation-hopeful-immunosuppressive-drug (see our literature review for more on islet cell transplantation).

- 2004 saw a 12% increase in BMY's R&D spending, including muraglitizar, which BMY expects to be one of three upcoming releases.
- According to management, BMY is "*more than half-way through a five-year period that will change our product portfolio."* Fightin' words! Let's hope they too are leaning toward even more investment in metabolic disease.
- Elliott Sigel, MD, PhD – BMY's Chief Scientific Officer, shared some interesting fodder:
    - Sigel commented that several years ago, BMY had 35 diseases in its pipeline. 35! This was too many, he conceded, so focus has been narrowed. There now exist ten current concentrations including, besides diabetes and obesity (which, excellently, appear to count for two), psychiatric disorders, Alzheimer's disease, atherosclerosis/thrombosis, HIV/AIDS, hepatitis, oncology, rheumatoid arthritis/related diseases, and solid organ transplantation.
    - Like many competitors, BMY claimed it was gaining strength through its collaborations with other companies on several projects across its disease portfolio. Although one could argue this is hype, they did partner with Merck on muraglitizar, after all, so it's probably valid to mention.
    - To improve compound success rates, BMY is focusing on the following. We *nearly* skipped this, because it sounds suspiciously of hype, but we ultimately bought it:
        - discovering the right targets
            - focusing on unmet needs
            - target validation
            - balance of target risk
        - developing the right compounds
            - early predictors of safety
            - back-up strategy
            - investigative toxicology
        - pursuing the right development plan
            - integration of science and marketing
            - collaboration with health authorities
            - leveraging the FDA's critical path initiatives
    - There's a better chance of getting approved if the market can tolerate some risk because there is little competition. This seems an odd thing to say in the midst of the Vioxx vortex, but there you have it.

- Okay, getting to the more focused commentary! Dick Gregg, V-P of Clinical Discovery, discussed muraglitizar
    - There is a significant unmet need in type 2 diabetes
        - Over 150m type 2 diabetes patients worldwide, he said. Actually, according to IDF, the number is pushing 200 million (194 million is their estimate, which excludes children).
        - Each year, over 4 million deaths occur worldwide from diabetes or its complications, such as atherosclerosis (this actually makes the U.S. estimate, ~200,000, pale in comparison).
        - Shortcomings of current therapies
            - Incomplete glycemic control
            - Lipid abnormalities common with diabetes not treated
            - *DCU note: We would add weight gain associated with nearly all other therapies, poor side effect profiles, relatively short therapy duration associated with many type 2 therapies, hypoglycemia associated with many other therapies, and need for several pills a day if therapy approaches comprehensiveness*
            - Note: we're not sure that it is a *shortcoming*, exactly, that current therapies don't treat lipids optimally (or at all). None of them claims to, for a start. But that was clever subtle (or not?) early marketing for muraglitizar.
    - Muraglitazar has a novel mechanism of action
        - PPAR-γ targets fat, increases insulin sensitivity, and reduces blood glucose.
        - PPAR-α targets the liver, decreasing free-fatty acid secretion, decreasing triglycerides and increasing HDL cholesterol.
    - Muraglitazar preclinical results
        - Two-year carcinogenicity studies were stated early and have been completed, helping to address current class concerns. Again, we're not sure if this addresses current class concerns – we think class concerns are still very much an open question – but certainly BMY benefits in being the only company to have completed these studies.
        - Incidences of tumors found in rodents were thoroughly investigated and found either to be "species-specific or to occur at levels 48x human exposure." It will be interesting to see what FDA thinks of this.
        - Data reviewed with FDA; long-term trials and submission to continue as planned. Following the meeting, muraglitazar was submitted to the FDA in December, 2004, consistent with expectations of a second-half submission.
    - Muraglitazar clinical program
        - Over 4500 patients participated in Phase I and II trials; more studies on-going (below)
        - Phase II study involving 1,477 patients taking multiple doses of muraglitazar vs. 15 mg pioglitazone (Actos).
        - Phase III study of 449 drug-naïve patients on 2.5 mg, 5 mg, and 5 mg open label.
        - Phase III study of 583 patients inadequately controlled on sulfonylureas taking muraglitazar 2.5 mg or 5 mg combined with a sulfonylurea.
        - Phase III study of 652 patients inadequately controlled on metformin taking muraglitazar 2.5 mg or 5 mg combined with metformin.
        - Phase III study of 1,159 patients inadequately controlled on metformin taking 5 mg muraglitazar vs 30 mg pioglitazone.
    - Key endpoints for all trials
        - A1C mean change from baseline
        - Triglycerides
        - HDL cholesterol
    - At the ADA in June 2005 – or earlier in publications – BMY will disclose results of all trials
        - In the first two studies mentioned above , 60% of patients taking muraglitazar as monotherapy reached the ADA goal A1C of ≤7.0%
        - 5 mg muraglitazar provides ADA target-level glycemic control for up to two years (Actos study) – two years is positive, though we are not certain of baseline A1C
    - Muraglitazar 5 mg achieved meaningful lipid lowering in both monotherapy and combination therapy trials.
        - Reduced triglycerides 26-29% from baseline.
        - Increased HDL 14-16% from baseline.

        - No change in LDL cholesterol.
    - Muraglitazar's safety and tolerability:
        - No clinical lab signals for liver or renal damage.
        - Weight gain and mild to moderate peripheral edema comparable with currently available PPAR-γ agonist drugs – we point out TZDs are not the best comparator. As TZDs do, muraglitazar may cause dose-dependent fluid retention that could lead to or exacerbate congestive heart failure (CHF). CHF was reversible with overall severity comparable to TZDs.
    - Muraglitazar's status:
        - Upcoming milestones:
            - NDA submission discussed (target of December 2004 was indeed met)
            - Presentation of Phase III data at ADA 2005
        - Initiating life cycle management program – interesting to hear this discussed, since the drug hasn't even been approved – clearly the R&D investment to date has been prodigious.
            - Titration trials
            - Comparator trials
            - Combination trials
    - Summary
        - Meaningful and durable effect on glycemic control in patients with type 2 diabetes – we look forward to more data on this.
        - Substantial improvement in lipid abnormalities typically associated with patients with type 2 diabetes – who knows, it's said that some diabetes drugs may ultimately wind up having greater CVD/lipid/other appeal.
        - Phase III data are now available for full evaluation of risk/benefit profile.
- LEA29Y: We mention this drug because although it is not directly relevant to diabetes at this stage, it may be valuable to the future of diabetes care if islet cell transplants ever do become integrated into clinical care.
- LEA29Y may address an unmet need in solid organ transplantation.
    - Two broad patient segments in solid organ transplantation:
        - 47,000 new transplant recipients/year
        - 326,000 maintenance patients
    - Initiation of Phase III trials for prevention of rejection in renal transplantation are targeted to begin shortly.
    - Calcineurin inhibitors (CNIs), current cornerstone therapies, have poor long-term outcomes.
        - Cardiovascular disease (CNIs can raise CVD risk; CVD is the leading cause of death among organ transplant recipients)
        - Chronic allograft nephropathy leading to graft loss
    - Target profile:
        - Co-stimulation blocker specifically engineered to provide greater efficacy in prevention of solid organ transplant rejection
        - Replacement for CNIs
        - Low incidence of acute rejection efficacy similar to cyclosporine
        - Improved cardiovascular/metabolic profile
        - Superior preservation of renal function, less chronic allograft nephropathy
        - Improved graft survival and long-term outcomes
    - Summary
        - Novel co-stimulation blocker
            - Prevention of graft rejection
            - Preservation of renal function in kidney transplant patients
        - Promising results in Phase II trials
        - Initiation of Phase III trials for prevention of rejection in renal transplantation are targeted to begin soon
        - BLA submission targeted for 2007/2008 in the U.S. and the EU

–by Melissa P. Ford and Kelly L. Close

5. New column-Glucose Patent Update: *Beginning with this issue of Diabetes Close Up, we will publish a periodic update of emerging intellectual property in the area of glucose monitoring. This survey will cover recent patents and applications in U.S., Europe, and world publications. A table will be provided listing all citations and statistics will be presented listing the number of citations in broad categories. In addition, several citations will be selected for a brief review and description. These updates are compiled and edited by D. Bommi Bommannan, PhD, JD, and Russell Potts, PhD. Who are they, you ask? (Well, many of you know them, but for those that don't…)*

D. Bommi Bommannan is medical device entrepreneur and a patent attorney. He most recently founded and runs MaxVal Group, Inc., a business founded on maximizing the value of patents. MaxVal helps clients build and maintain patent portfolios relating to medical devices and also provides patent licensing and acquisition services. Russ Potts was formerly VP of R&D at Cygnus, where he helped develop the GlucoWatch Biographer. He currently heads a consulting company (Russ Potts Consulting, LLC) in San Francisco focused on glucose monitoring and other medical devices, as well as transdermal drug delivery products. They can be contacted at bommi@maxvalgroup.com and russ@vosspotts.org, respectively.

Glucose monitoring patents and patent applications published in January, 2005: A search of US, European and World patents and applications related to glucose monitoring yielded more than 60 citations for January 2005. The citations are shown in Table 1. These citations were categorized into those:

(1) related to noninvasive or minimally invasive techniques (N/M);
(2) using subcutaneous implants for continuous monitoring (S/C), and
(3) using blood or other bodily fluids, such as interstitial fluids (B/F).

The results showed that about 65% of all patents and applications were in the bodily fluids (B/F) category, while about 25% was found in the minimally invasive (N/M) category. Only about 10% was found in the S/C category.

We have selected several interesting patents from January 2005 which are summarized below.

Automatic, periodic blood glucose measurements
US Patent Application 20050011759 by Moermann, McAleer and Steine (Assignee: not disclosed) describes a watch-like device that automatically provides single-step operation in which sample acquisition and analysis. The apparatus is specifically for detection and measurement of an electrochemically-detectable analyte, such as glucose, in blood or interstitial fluid, and includes a meter unit, a lancet and an electrochemical sensor. Moreover, the device can be repeatedly used to obtain a series of glucose measurements.

Sample Claim:
42. An apparatus for detection and quantitation of an electrochemically-detectable analyte in a sample of blood or interstitial fluid comprising: a housing: a plurality of electrochemical sensors on a disk positioned in said housing, each of said electrochemical sensors comprising an absorptive member for the uptake of a sample of blood or interstitial fluid; an equal plurality of cutting members in said housing each of said cutting members being associated with at least one of said electrochemical sensors; a plunger said plunger sequentially engaging one of the cutting members and moving said engaged cutting member in a cycle from an initial position to a piercing position the electrochemical sensor being disposed such that the plunger causes the cutting member to pierce the skin of the user adjacent the absorptive member said absorptive member taking up a sample from the pierced skin of the user when it is pierced by the lancet without movement of the apparatus; a connector disposed within said housing for engaging one of said electrochemical sensors and transmitting a signal from said engaged sensor indicative of an amount of analyte in said sample; and a display operatively-associated with said engaged connector said display adapted to display the amount of the analyte to a user.

The claims are for devices that can combine the lancing, sample collecting and sensing in a one-step operation and to allow "in situ" sampling without movement of the apparatus. The apparatus could be in the form of a disk with multiple sensors, each with an absorptive material to uptake blood or interstitial fluid; an equal number of cutting members associated with each sensor; a plunger to allow the cutting member to pierce the skin to obtain separate samples for each sensor; a connector to transmit signal from the engaged sensor; and a display. In one claimed

embodiment the device is "watch-like". Furthermore, the watch-like device can have a timer to allow automatic sample evaluation at pre-determined intervals, as well as alarms to signal high or low levels.

Glucose measurement in ocular fluid
US Patent 6,850,786 (Assignee: Novartis AG) describes the measurement of an analyte in ocular fluid using an ophthalmic lens. The lens contains fluorescent compounds, whose emission properties change with analyte binding. The lens is interrogated by an optical source and the fluorescence emission is recorded. When glucose-specific derivatives are used, the change in fluorescence intensity is directly related to glucose concentration.

Sample claim:
Claim 1. An ophthalmic sensor for detecting an analyte in an ocular fluid, comprising:
an ophthalmic lens; and
one or more detection reagents for said analyte in and/or on said ophthalmic lens, wherein the detection reagents comprise a receptor moiety and a fluorescent moiety wherein the receptor moiety comprises an analyte/competitor moiety binding site at which the analyte can reversibly bind, and wherein the fluorescent moiety in cooperation with the receptor moiety provides a detection of the analyte.

The ophthalmic lens could be a contact lens, an intraocular lens, a subconjunctival lens, an intracorneal lens and a shunt or implant that can rest in the cul de sac of the eye. The detection reagents comprise a receptor and a fluorescent moiety for detection of an analyte. The use of boronic acid derivatives for the detection of glucose is specifically claimed.

Noninvasive glucose measurement
World patent application WO2005004712 (Assignee: Glucon) describes a "wearable glucometer" for assaying an analyte in blood in a blood vessel below a patient's skin. The device is intended for continuous, noninvasive measurement. The device uses light of at least two wavelengths; one for locating a blood vessel and a second for assaying the analyte within the blood vessel.

Sample claim:
Claim 1: Apparatus for assaying an analyte in blood in a blood vessel below a patient's skin comprising: at least one light source controllable to transmit light into tissue below the skin through at least one first region on the skin; at least one light detector that receives a portion of the transmitted light that reaches at least one second region on the skin after propagating through the blood vessel and generates signals responsive to the received light; and a controller; wherein the controller controls the at least one light source to transmit light at at least one wavelength that interacts with blood and at at least one wavelength that interacts with the analyte and uses the signals responsive to the light that interacts with the blood to determine a location for the blood vessel and the determined location and signals responsive to the light to assay the analyte.

The device also claims a "modulation apparatus" (using ultrasound, mechanical pressure or an electric field) to modulate blood flow and thereby modulate the corresponding signal. This modulation allows location of the blood vessel for subsequent analysis. Glucose is claimed as a specific analyte.

See appendix for table of glucose monitoring patents and patent applications published in January, 2005.

–by D. Bommi Bommannan, PhD, JD, and Russell Potts, PhD.

6. Errata & etc.
In our last issue, I must have been hypoglycemic when writing about Symlin – I said that our estimates were *below* the Street estimates. Since our commentary was positive, that probably came as a non sequitur. Indeed – our estimates would be higher than the Street's estimates – peak sales seem to top out at only a bit upwards of $200m and it's only a very few analysts that go that far. We can see an argument that peak sales would be twice as high or higher – assume pricing is $90/month (we have no idea, but we think at least $3/day and perhaps more is eminently reasonable given there are no competitive drugs and TZDs are commonly priced at $4/pill), and that 10% of type 1 patients and 5% of type 2 patients on insulin would take Symlin, and you're already there! For us, that is believable. Yes, there are difficult aspects about the drug – it's an injection (but all potential users are used to that) and it's

variable dosing (see previous parenthetical) – but remember, type 1 patients in particular have had no new drugs since insulin analogs, *and* although the A1C impact may not be major, there appears to be considerably less glycemic variability with Symlin use. That's what patients care about – glucose status is becoming an increasingly important idea, versus just A1C – and Symlin should benefit as a result. Oh, and I almost forgot! Almost everyone seems to lose weight on Symlin – that's among the most consistent of all the side effects. In America, you couldn't ask for a greater blessing in the side-effects listing! Although marketing would not be pursued on this basis, this will be discussed among patients as a positive side effect (recall this group of chronic patients communicates quickly and frequently with one another).

Appendix: Glucose monitoring patents and patent applications published in January, 2005

Publication	Title	Assignee	Priority
EP1035799B1	APPARATUS FOR OBTAINING INTERSTITIAL FLUID FOR DIAGNOSTIC TESTS	Abbott Laboratories	1997-12-02
US6837858	Method and apparatus for obtaining blood for diagnostic tests	Abbott Laboratories	1996-12-06
US6841052	Electrochemical-sensor design	Bayer Corporation	1999-08-02
WO05001447A1	IR-ATR-BASED PROCESS AND APPARATUS FOR ANALYSING VERY SMALL AMOUNTS OF SAMPLE IN THE NANOLITER RANGE	BAYER HEALTHCARE LLC	2003-06-27
WO05000114A2	PORTABLE MEDICAL DIAGNOSTIC APPARATUS	BAYER HEALTHCARE LLC	2003-06-03
WO05001680A1	USER INTERFACE FOR PORTABLE MEDICAL DIAGNOSTIC APPARATUS AND METHOD OF USING THE SAME	BAYER HEALTHCARE, LLC	2003-06-03
WO05001463A1	VOLTAMMETRIC DETECTION OF METABOLITES IN PHYSIOLOGICAL FLUIDS	CRANFIELD UNIVERSITY	2003-06-26
US6850790	Monitoring of physiological analytes	Cygnus, Inc.	
US20050010093A1	Formulation and manipulation of databases of analyte and associated values	Cygnus, Inc.	2000-08-18
USRE38681	Electrode with improved signal to noise ratio	Cygnus, Inc.	1997-03-25
USRE38688	Sheet-like diagnostic device	Dade Behring Marburg GmbH	1984-12-15
US6846288	Photoacoustic assay and imaging system	Glucon Inc.	2000-08-24
US6841389	Method of determining concentration of glucose in blood	GlucoSens, Inc.	2001-02-05
WO05004712A1	WEARABLE GLUCOMETER	GLUCON INC.	2003-07-09
WO05005974A1	STRUCTURE AND MANUFACTURING METHOD OF DISPOSABLE ELECTROCHEMICAL SENSOR STRIP	HUANG, Alice, Y.	2003-06-17
US6839584	Method and apparatus for minimizing spectral interference due to within and between sample variations during in-situ spectral sampling of tissue	Instrumentation Metrics, Inc.	2000-05-02
US6844149	Method, system, and apparatus for measurement and recording of blood chemistry and other physiological measurements	International Business Machines Corporation	2001-06-29
US6847451	Apparatuses and methods for analyte concentration determination	LifeScan, Inc.	2002-05-01
US6837988	Biological fluid sampling and analyte measurement devices and methods	LifeScan, Inc.	2001-06-12
US20050010269A1	Microprocessor controlled ambulatory medical apparatus with hand held communication device	Medical Research Group, Inc.	2000-01-21
US20050004439A1	Real time self-adjusting calibration algorithm	Medtronic MiniMed, Inc.	2000-02-23
US20050020895A1	Atraumatic sensor lead assemblies	Medtronic, Inc.	
US6837976	Disposable sensor with enhanced sample port	Nova Biomedical	2002-04-19

Publication	Title	Assignee	Priority
	inlet	Corporation	
US6850786	Ocular analyte sensor	Novartis AG	
WO05001418A2	METHOD AND APPARATUS FOR BODY FLUID SAMPLING AND ANALYTE SENSING	PELIKAN TECHNOLOGIES, INC.	2003-05-30
US6849237	Body fluid test apparatus with detachably mounted portable tester	Polymer Technology Systems, Inc.	
US20050003523A1	Test strip for determining concentration of multiple analytes in a single fluid sample	Polymer Technology Systems, Inc.	2001-12-28
WO05001474A1	SYSTEM AND METHOD FOR CODING INFORMATION ON A BIOSENSOR TEST STRIP	ROCHE DIAGNOSTICS GMBH	2003-06-20
WO05001462A1	SYSTEM AND METHOD FOR DETERMINING AN ABUSED SENSOR DURING ANALYTE MEASUREMENT IN A BIOLOGICAL FLUID	ROCHE DIAGNOSTICS, GMBH.	2003-06-20
EP1496350A2	Method and apparatus for generating basis sets for use in spectroscopic analysis	Sensys Medical, Inc.	1997-08-14
WO05007879A1	IN VIVO CALIBRATION METHOD FOR SUBCUTANEOUS AMPEROMETRIC GLUCOSE SENSORS AND SYSTEM THEREFOR	SEOUL NATIONAL UNIVERSITY INDUSTRY FOUNDATION	2003-07-22
US20050009126A1	Method and apparatus for providing power management in data communication systems	TheraSense, Inc.	2003-06-12
WO05001522A2	MEASUREMENTS OF OPTICAL INHOMOGENEITY AND OTHER PROPERTIES IN SUBSTANCES USING PROPAGATION MODES OF LIGHT	TOMOPHASE CORPORATION	2003-06-04
US20050010087A1	Wireless, internet-based medical-diagnostic system	Triage Data Networks	2003-01-07
WO05000109A2	QUATERNARY NITROGEN HETEROCYCLIC COMPOUNDS FOR DETECTING AQUEOUS MONOSACCHARIDES IN PHYSIOLOGICAL FLUIDS	UNIVERSITY OF MARYLAND BIOTECHNOLOGY INSTITUTE	2003-06-27
EP1498070A1	NONINVASIVE BLOOD COMPONENT VALUE MEASURING INSTRUMENT AND METHOD	Yamakoshi, Ken-ichi	2002-03-25
US20050021066A1	Analytical device with lancet and test element		2001-08-29
US20050020893A1	Optical spectroscopy pathlength measurement system		
US20050020892A1	Compact apparatus for noninvasive measurement of glucose through near-infrared spectroscopy		
US20050019953A1	System and method for coding information on a biosensor test strip		
US20050019945A1	System and method for coding information on a biosensor test strip		
US20050019848A1	Blood sugar tester and data uploading method		2002-05-14

Publication	Title	Assignee	Priority
US20050019805A1	System and method for coding information on a biosensor test strip		
US20050018202A1	Measurements of optical inhomogeneity and other properties in substances using propagation modes of light		
US20050016846A1	System and method for coding information on a biosensor test strip		
US20050016845A1	System and method for coding information on a biosensor test strip		
US20050014997A1	Method of sample control and calibration adjustment for use with a noninvasive analyzer		1997-08-14
US20050014290A1	Binding proteins as biosensors		2002-01-04
US20050014213A1	Method of colorimetry and reagent for use therein		2001-12-28
US20050013731A1	Test strip with slot vent opening		2003-06-20
US20050011759A1	Combined lancet and electrochemical analyte-testing apparatus		2000-03-02
US20050010134A1	Blood and interstitial fluid sampling device		1996-05-17
US20050010092A1	Method and apparatus for reducing coupling between signals		2003-07-08
US20050010091A1	Non-invasive measurement of blood glucose using retinal imaging		2003-06-10
US20050010090A1	Compact apparatus for noninvasive measurement of glucose through near-infrared spectroscopy		2002-03-08
US20050009130A1	Castable diffusion membrane for enzyme-based sensor application		2003-07-11
US20050004494A1	Lancet device having capillary action		2001-01-22
US20050004438A1	Compound metal analyte sensor		2003-06-16
US20050004324A1	Permselective structurally robust membrane material		2003-05-21
US20050002031A1	Method and device for determining a light transport parameter in a biological matrix		2001-12-22
US20050002018A1	Body fluid analyte measurement		1999-03-09
US20050000806A1	Biosensor for monitoring an analyte content with a partial voltage generated therefrom		2003-07-01

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