DIABETES CLOSE UP

Diabetes Close Up, V3, #6
March 17, 2004

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

1. **Happy St. Patrick's Day**!
2. **Two FDA reports –** see Appendix A, page 2-4.
    a. Part 1: Yesterday's report "*Innovation Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*" may have interesting implications for diabetes.
    b. Part 2: Last week's report on obesity "*Calories Count*" – less than compelling.
3. **Cowen Conference**: SG Cowen had a terrific investment conference in Boston last week; see highlights in Appendix B, page 5-8, on Medtronic, Lilly, Novartis, and others. In particular, the diabetes panel with Drs. Charles Clark (Indiana University) and George King (Joslin Clinic) was outstanding. In the standing-room-only (big!) ballroom, the good doctors mused on everything from inhaled insulin (decidedly negative) to the growth of type 2 diabetes ("*patients are walking time bombs*") to dual PPARS ("*very exciting - ….and we're waiting for a trial to show these are anti-atherogenic*…") to DPP-IVs ("*probably not a more effective and safe method of regulating GLP-1 than administering a GLP-1 analog*") to Lantus' impact on insulin pump prescription ("*No impact*" they said, flatly) to timing of continuous sensor technology (5-10 years for a serious impact – then again, what does serious mean? Taking even 10% share of the most profitable episodic monitoring customers could enable blockbuster sales results for the category.)
4. **Obesity roundup**: All this obesity news is frankly exhausting, no? Information is good, but now, now, we have enough information. Let's focus on action, pun intended – the energy equation is theoretically simple; so let's look at how to change behavior. See Appendix C, page 9-11 for a review of obesity news to date in 2004, along with an in-depth look at the US's official objection to WHO's plan to halt obesity, which we see as an, um, suboptimal approach to the issue.
5. **Media Roundup**: Numerous peer-reviewed pieces of note, and a cool documentary - see Appendix D.
    a. Diabetes Care, March, 2004 – two key pieces of note: 1) *Improved Glucose Excursions Using an Implantable Real-Time Continuous Glucose Sensor in Adults With Type 1 Diabetes"*: DexCom's first published results are the March *Diabetes Care*; and 2) Dr. David Klonoff's *Editorial, The Need for Separate Performance Goals for Glucose Sensors in the Hypoglycemic, Normoglycemic, and Hyperglycemic Ranges*.
    b. Super Size Me – In this novel documentary, the director seeks to find out what happens when McDonald's is eaten three times a day for 30 days straight.
6. **ADA preview/other conferences**: This time of year is so exciting, as the schedules start to come out for all the major conferences. We're at Diabetes 2004 UK (www.diabetes.ork.uk/apc) starting today, in Birmingham, England; then we've got the UCSF diabetes update (www.medicine.ucsf.edu/cme) and AACE (www.aace.com) next month, ADA Southeastern in May, ADA in June (both www.diabetes.org), AADE (www.aadenet.org) in August, and EASD (www.easd.org) in September. Preview highlights, coming soon.
7. **Observations**:
    a. **Diabetes 2004**! This is now available; see our website www.closeconcerns.com. Please let us know if you'd like to receive the table of contents.
    b. **St. Patrick's Day** Hope you have had a wonderful day; even though I changed my name from Shaughnessy to Close three years back, I still consider this one of the most important holidays of the year! I'm thinking today fondly of my grandfather, father, brother, and cousin all named Patrick. Great name, isn't it – Patrick Shaughnessy!

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

Appendix A: The FDA's Latest …

Part 1: The FDA on "Innovation Stagnation"

The FDA put out a new report yesterday, *"Innovation Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products"* on ways to speed drugs to market. I'm not sure how much is rhetoric, but the main finding appears to be that the medical product development process is no longer able to keep up with basic science innovation. (What's that old saying about acknowledgement being the first step to change? Hopefully we've moved out of the state of denial.) A concerted effort is obviously needed to apply the new biomedical science to medical product development, which would enable faster, more successful drug development. A few points of interest directly or indirectly related to diabetes and/or obesity, clearly the major public health issues of the moment:

1. **The FDA notes a basic disconnect between discovery and product development**. FDA is now planning an initiative that will identify and prioritize 1) the most pressing development problems and 2) the areas that provide the biggest opportunities for rapid improvement and public health benefits. Theoretically, this bodes well for diabetes, so I'd view it as a positive; although it's unclear how quickly the agency will act in practice.
2. **If there's any doubt that we're at a troubling point**, see Figures 1 and 2 in the report, which can be found at www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf - Figure 1 shows how pharma and NIH spending has increased substantially over the last decade, while major drug and BLA submissions have plummeted. Indeed, the contrast is striking, and while we all know these numbers, actually looking at the trend over the past decade is sobering. The slowdown in medical device submissions is also highlighted.
3. **An analysis by Windhover and Bain show that from 1995-2000, the estimated cost of taking a drug from discovery phase to launch was $1.1 billion; from 2000-2002, this estimate rose to an alarming $1.7 billion.** While the latter figure may be skewed due to a small number of approved drugs, it is still quite disturbing. Unsurprisingly, the majority of the increased costs over that short time period stem from Phase III and launch expenses. The report implies that many more drugs should be killed earlier in the process, and that the FDA alone has valuable information that could make that happen.
4. **FDA reviewers, they say, are in a unique position to help identify common themes and systematic weaknesses in similar products and can draw key lessons from what they find. I'd love to see this report - as yet, it too appears to be theoretical**.
5. **Areas with guidance documents are said to be nearly twice as likely to be approved after the initial review process and are approved in a third less time**. Stay tuned – a guidance document is in the works for weight loss drugs (see Appendix A, part 2).
6. **The agency says there is an urgent need for improvement in efficiency and effectiveness of the clinical trial process**, including improved trial design, endpoints, and analyses. They claim they will address this in "roadmap" efforts, which I would take as a cautiously positive sign, depending on how fast they can work.
7. **The report quotes an article in which an official from Pfizer notes that liver toxicity alone has cost them over $2 billion in the last decade**. This of course is an oblique reference to Rezulin. While the FDA seems to suggest that this is solely due to an unforeseen safety issue, I would argue that it is more complex; that labels weren't followed, patients were not always getting tested when asked to, and doctors weren't able to spend enough time with patients discussing tests[1].
8. **The report offers examples of tools that are urgently needed, namely methods to further enhance the safety of transplanted human tissues** (others listed are better predictors of human immune responses to foreign antigens and new techniques for assessing drug liver toxicity). I would view this

[1] I had a letter published in the *New York Times* business section on Sunday, March 6, 2004 responding to a February 29, 2004 piece entitled "*Is Biotechnology Losing Its Nerve*?" Unfortunately, the NYT doesn't include letters on its website but let us know if you'd like a copy and we will send it to you.

as a potential positive on the islet cell front, though cell source supply (with immunosuppression in second place) still represents a major challenge.

9. **The report also stresses that more focus is needed on industrialization challenges** - many product failures during development are ultimately attributable to problems relating to the transition from lab prototype to industrial product, the report notes.
10. **The FDA highlights progress in blood glucose monitoring as a success for the country's patients with diabetes, emphasizing that numerous *new* devices are being developed for blood glucose monitoring**. I would take as a successful sign, as one of these - TheraSense's Navigator – is at the agency now and Medtronic's Guardian 2 should be submitted shortly. I can't imagine if prospects were poor for continuous monitoring that they would highlight, even in sideways fashion, the new technology. In terms of their success, the report reference the fact that separate accuracy and precision goals were defined for extreme ranges to keep pace with changing clinical demands for tighter glucose measurement. (True, although the ranges probably aren't extreme enough, per Dr. David Klonoff's impressive editorial in this month's Diabetes Care – see Appendix D, Media Roundup.)
11. **A quick follow up - I was surprised and disappointed to see the report reference "the country's 16 million diabetics" - this statistic is flipping two years outdated**! The current estimate exceeds 18 million (I sent them an e-mail referring them to the CDC website) - while the agency frequently stresses how committed it is to diabetes, this won't heighten confidence.
12. **Also of potential importance to the blood glucose monitoring front, the report says that "additional characterization procedures and standards ... for implanted drug-device combinations are urgently needed**." This will be interesting to watch as work progresses on the artificial pancreas front.
13. **Ultimately, I would be cautious about interpreting this report as a real positive**; for now, I would stand aside and watch how things play out. The report does appear to heighten the urgency with drug development and hopefully this will play out to our collective benefit: *"...If we do not work together to find fundamentally faster, more predictable, and less costly ways to turn good biomedical ideas into safe and effective treatments, the hoped-for benefits of the biomedical century may not come to pass or may not be affordable*..." Exactly! Let's push for moving rhetoric into real action.

Part Two: The FDA on Obesity

So the FDA published a long-awaited obesity report last week http://www.fda.gov/oc/initiatives/obesity/. I'm not going to spend much time on this report because in my view it's not worth it. Suffice to say, I did not find this 39-page piece particularly compelling at first read (the references are the best part). Why? There is just not a lot of conviction in the report about what should happen; mostly, it "encourages" food companies and restaurants to do things like make new labels with bigger font for calories (sort of strange, it's written as if it's a new idea), give nutrition information on menus (I know it's expensive for restaurants to do this and I sympathize, but how about a plan, even over the next decade, to enforce this rather than just suggest it?) and "encourages" consumers to eat less and exercise more (ah yes, the old energy equation. We know it backwards and forwards.) At first glance, to say the least, I would not imagine that obesity is going to decline in the near or long term as a result of the report. While I realize that we need to tread carefully here – admittedly, a lot of ideas I like are costly – I think it's shameful that it took them this long to come up with most of these ideas. The one great thing is some new advertising – see http://www.adcouncil.org/campaigns/healthy_lifestyles/. These are excellent ads – apparently the government is spending about $1.0 million on them – won't come close to the billions spent by fast food and soft drinks, but it's a start!

Some *other* ideas the report doesn't explore:

1. How about looking further into a fat tax? Possibly unpopular and maybe even wrong, but I bet it would have some serious impact – look what taxes did for tobacco use.
2. How about if insurance gave people a break for good cholesterol scores, achieving and maintaining weight loss, achieving and maintaining better A1Cs, etc? Yes, costly to track, but people do anything for a deal.
3. How about if the government subsidized gym expenses?
4. How about mandating over time no sugar-sweetened drinks in schools? Put water bottles in those machines.

5. How about mandating, again, over time, more physical activity both at home and work, and here's the rub, think creatively about how to reward people. I attended recently an AHA symposium on "*Prevention of Overweight and Its Consequences Beginning in Youth*" where USC exercise expert Dr. Russell Pate pointed out that while 13% of American schoolchildren get to school in a "non-mechanical" way – i.e., walking or biking – in Australia, that figure climbs to 43%, and in Denmark and Germany, to 60% and 85%, respectively. The worst thing? Pate thinks 13% is an overestimate!
6. How about even simple things, like signs reminding people to take the stairs?

The main item of note with possible industry implications was a recommendation to revise and reissue the FDA's 1996 draft guidance for the clinical evaluation of weight-control drugs. "*This action item reflects the fact that some obese and extremely obese individuals are likely to need medical intervention to reduce weight and mitigate associated diseases and other adverse health effects. FDA would issue this revised guidance for public comment*." It may take eons to emerge, but this is one to watch for.

-- by Kelly Close

Appendix B: SG Cowen Conference Review

Fantastic! I found the SG Cowen conference an extremely impressive investment conference. Many of you know that they bring in loads of experts and do series of panels on various therapeutic areas. The panel on diabetes was excellent, as the doctors spoke very candidly. Although it's true that Drs. Charles Clark and George King represent two viewpoints only, two very highly regarded viewpoints at that. A summary of my interpretation of their most interesting points follows. The companies may have been a bit less transparent than the doctors but here, too, an interpretation of nuggets of interest is noted below.

SG Cowen analysts started off the session by reeling off some statistics on the diabetes front:

1. **Drugs related to diabetes achieved $13 billion in worldwide sales last year and should reach $20 billion by 2008** (10% compound growth).

	Compound	2003 sales	2008E sales
a.	Insulin	$4.7 billion	$ 9.3 billion
b.	Glitazones	$3.6 billion	$ 6.3 billion
c.	Sulfonylureas	$1.0 billion	$ 1.2 billion
d.	Other	$3.7 billion	$ 3.2 billion

2. **Revenue is concentrated**; sales by Novo, Takeda, Eli Lilly, and Glaxo represent 68% of the total. Diabetes is most key to Novo and Takeda in terms of overall product portfolios.
3. **Trends**:
    a. Insulin will become a more primary treatment – insulin sales should double over next five years, capturing nearly 50% of the diabetes drug market for.
    b. Glitazones have been and will continue to be big, as they delay the onset of insulin requirements, which is still a major goal for many type 2 patients.
    c. Dual PPARS will be key to watch, especially for lipid management.
    d. Inhaled insulin could further expand the insulin market, but long-term safety is still a stock overhang.
    e. Emerging GLP-1 compounds have terrific physiological profile and broad use between these agents and insulin is expected.
4. **Survey highlights**: As part of the conference, panelists and audiences participated in real-time voting on a range of questions. This is always excellent fun. At the diabetes panel, a discussion with Drs. Clark and King ensued. King, by the way, is one of the patent holders in an exciting area, the PKC beta inhibitor[2].
    a. **Dual PPARs**:
        i. The most promising dual PPAR is being developed either by AstraZeneca or Eli Lilly, according to the good doctors. 24% of the audience chose BMS.
        ii. New PPARs in the clinic are promising in light of potential benefits related to lipid modulation, glucose reduction, body weight reduction, and relative side effect profile.
        iii. Both of the doctors believed that newer glitazones offered key advantages over Avandia and Actos.
        iv. Innovation in this area is very exciting, said Dr. King. Most PPARS are dual agnostics, meaning they have lipid and other advantages, and they may be anti-atherogenic. The animal data is strong, but we are still waiting for larger trial data.
        v. On current TZD agonists: 16% of people on insulin have fluid accumulation that could be clinically significant, said Dr. King.
        vi. Dr. Clark expressed enthusiasm about the drugs. Type 2 patients are "*a walking time bomb for cardiovascular disease*," he said, noting that they take two to three pills each for blood glucose, hypertension, lipids, etc. If we can have drugs do some or all of this, it would be promising.
        vii. Side effects may be an issue – edema noted.

[2] PKC-beta (protein kinase C-beta) mechanism of action increases new blood vessel formation.

viii. These new drugs won't take over in 3-5 years, but in 5-8 years, we'll see some movement.

b. **GLP-1**:
   i. According to the majority of the audience, once approved, Exenatide will be used in up to 25% of patients with diabetes.
   ii. One doctor agreed, while the other thought it could be used in a whopping 51-75% of patients with diabetes.
   iii. Clearly anything close to 25% share would be a major hit, to say nothing of the higher percentages.
   iv. Both doctors felt that the LAR was likely to at least modestly improve efficacy, convenience, and market penetration.
   v. As more and more patients go on insulin, more may choose GLP-1 after it's approved, due to potential weight loss, versus weight gain.
   vi. Regarding prospects for Novo's NN2211, the doctors' felt this was probably a good drug, and pointed out that Novo is a "*potent*" marketer.
   vii. Despite the promise, daily shots are still an issue. Dr. King noted that this is a behavioral issue for some patients; "*…once they progress to shots, they feel they have a serious disease – there can be many cultural barriers*."

c. **DPP-IV**:
   i. Both doctors felt that inhibition of DPP-IV would probably *not* prove to be a more effective and safe method of regulating GLP-1 than administering a GLP-1 analog, while 59% of the audience thought that it would or probably would.
   ii. The doctors were split on whether Novartis or Merck had the more promising compound – the audience voted for Novartis, 4-to-1.
   iii. "*Novartis is about to go to phase 3, and go head to head trial with (some unnamed agent), looking for equivalency. If this happens, they'll be ahead …*"

d. **Ruboxistaurin**:
   i. The doctors both felt that Lilly's would gain approval for neuropathy and ophthalmology applications, but not necessarily for nephropathy.
   ii. The neuropathy study should be done in 2004.
   iii. J&J, it was said, is working on a compound in this area, as is Novartis, and "*there may even be a fourth*".

e. **Insulin**:
   i. "We will see more and more insulin use here in the US," said Dr. Clark. In Europe, about 42% of type 2 patients use insulin, compared to ~25-27% here, but he believes that Lantus has helped more and more physicians in this country feel comfortable prescribing insulin. This makes sense, because there's less hypoglycemia with Lantus, which is a pain in the neck. It is also pretty easy to teach and learn, especially once-per-day usage, although it seems there are probably plenty of patients on one shot a day that should be taking prandial insulin, as has been pointed out recently by key thought leaders.
   ii. Lantus current share of the insulin market is 22% - both doctors felt this would increase to 25-40% over time. Most of the audience agreed.
   i. In terms of impact on pump therapy, both doctors said Lantus had no impact on their willingness to prescribe pumps, though 67% of the audience had expected it would have had a moderate impact. My take: we've turned the corner on Lantus being a barrier – the benefit to getting patients used to basal/bolus therapy now outweighs the belief that Lantus can do everything a pump can do. I believe this is because while some patients have uniform basal profiles, most do not, so problems with Lantus can emerge with dawn phenomenon, exercise, etc. No question that Lantus is better than NPH or the other older, less stable insulins, however – the product has enabled great strides in diabetes management. I also believe, however, that the new smarter pumps, which also happen to be smaller, more aesthetically pleasing, etc., will also prompt greater penetration of this market.

ii. On the oral insulin front, various challenges were discussed, including bioavailability/efficacy, dosing reproducibility, speed of onset/duration of action, and long-term safety. The doctors were split on what represented the biggest challenge, with one opting for bioavailability/efficacy and the other choosing long-term safety.

f. **Inhaled insulin**:
   i. Both doctors felt that inhaled insulin side effects, including pulmonary function declines, antibody formation, and cough, would delay Exubera approval by 3-5 years. Both wanted longer-term data.
      1. Said Dr. Clark: "*I am not a fan. 31-gauge works*…" referring to Becton Dickinson's 31-gauge, nearly painless syringes. He added that some subset of patients will definitely have adverse events, and it's not possible to identify that until it happens – the implication being there's a decent chance it doesn't happen until after approval, a la Rezulin. Long-term fibrosis is difficult to reverse (can take ~5-10 years).
      2. Insulin has two types of action, acute and chronic, and Dr. King noted that the second one is fairly unpredictable.
      3. The doctors allowed that it would be a great product for truly needle-phobic patients.
      4. Lilly is in second place in the horse race – they are thought to have an advantage in that they already take insulin. If Lilly has an effective method, it may have a pricing advantage, because of higher bioavailability. It was said that Lilly is trying to convince healthcare professionals that the powder form is a longer acting hormone. The highest bioavailability I've heard of is with Mannkind's inhaled insulin.
      5. In conclusion, "*Inhaled insulin is really not a big deal…" at* the major meetings.
   ii. The audience was more updated on approval likelihood, though not necessary on uptake: 42% felt the side effect would delay approval by 1-2 years, and 41% thought it would not delay FDA approval beyond 2005. Of the 41% who felt it wouldn't delay approval, 37% felt that the side effect profile would have a limited impact on uptake, while 63% felt it would have a significant impact.
   iii. If proven safe, inhaled insulin would be used in up to 20% of type 2 patients with diabetes in the U.S., according to the doctors. For type 1 patients, one doctor felt it would be used in fewer than 10% of this population, while the other thought perhaps 21-30% would use it. Although it may seem counterintuitive that a higher percent of type 1s would use versus type 2s, Dr. Clark pointed out that only 26% of the current type 2 population in the US takes insulin (far lower than in Europe and expected to move higher in the US according to Dr. Clark) so even if half this population moves to inhaled insulin that's still only 10-15% of the total type 2 population if these percentages stay constant. 35% of the audience felt that inhaled insulin would be used in over 20% of type 2 patient population.
   iv. The doctors pointed out that their colleagues do not want to give a new class of drug for which the side effect profile will be uncertain for 10-15 years.

g. **Misc: Continuous monitoring**/LDL/anti-CD3:
   i. While half the audience felt that continuous glucose sensor technology would likely impact the market in fewer than five years (not clear exactly what impact means, but I think most took it to mean a significant share), both doctors felt it would take 5-10 years. Both doctors felt it was probably true that continuous glucose sensors would not replace conventional meter and strip testing. Just as in today's market, there is room for a number of brands, I think the same will be true once continuous monitoring is proven, and particularly once it's reimbursed.
   ii. Dr. Clark noted that blood glucose monitoring is the most frustrating aspect of diabetes treatment for doctors, as it requires huge motivation for patients.

iii. Recent data from the PROVEIT trial showed the lower the LDL, the better. Squirrels have LDL of 35.

iv. On anti-CD3 - the question is: Do these new immunosuppressants last? One sentiment was that they may work for a few months to a year, but the action may not persist.

-- By Kelly Close

Company points of note:

1. **Medtronic**:
    a. No comments on diabetes. Is that in itself a comment, some asked? No, a lot just happened at ACC. Roughly 90% of the discussion surrounded CRM, with the rest addressing the vascular business.
    b. One interesting (albeit highly tangential) note was MDT's focus on telemetry. The company appears to be making an enormous push into telemetry technology – allowing doctors to monitor/adjust CRM devices without the patient visiting the office (through Internet/phone line telemetry). The company believes this will be a major competitive advantage. It is certainly possible that MDT could build on this (presumably) positive experience and push the telemetry angle into diabetes care; there certainly may be some opportunity/demand for CDEs to monitor patient glucose control on remote basis.
2. **Eli Lilly**:
    a. Ruboxistaurin, or PKC-beta inhibitor, targets underlying microvascular damage associated with microvascular complications, specifically diabetic neuropathy, diabetic retinopathy, and diabetic nephropathy. Ruboxistaurin's first indication will be for neuropathy; phase 2 data looked good and filing is expected for 2H05.
    b. Cagily, the company noted that its PPAR modulator may have a positive balance between gamma and alpha PPAR receptors, which could allow it to address both insulin sensitivity and lipid metabolism.
    c. Least was said about exenatide, the GLP-1 that is expected to be submitted by mid-year.
    d. Humalog reached $1.0 billion in 2003 (Ed. note: with the help of price increases).
3. **Novartis**:
    a. Look for filing of Sandostatin LAR (retinopathy) in '05, and LAF237 (DPP-IV) in '06.
4. **Eyetech**:
    a. Expecting phase 2 data for diabetic macular edema in mid-04.
    b. The data looks good; importantly, the company has no competition, and to boot, the any improvement in eyesight is meaningful to patients. Onward!
5. **Nektar**:
    a. Look for a US filing of inhaled insulin in late 2004.
6. **Aradigm**:
    a. Aradigm clearly believes liquid inhaled insulin formulations are better because results are more consistently reproducible, the aerosol quality is higher, and the formulation is more tolerant of "abuse" during shelf-time.
7. **Alkermes**:
    a. As expected, Exenatide LAR Phase 2 results will be released in 2H04. The AIR Insulin product is currently in Phase 2 studies (in Type 1 patients) and partner Lilly will make a go/no-go decision in 3Q04. The powder-based inhaler looks small and elegant, reminiscent of a Flash memory drive. Panelists felt that Lilly may have a cost advantage.
8. **Kos Pharma**:
    a. The company's priority is clearly on cholesterol. Kos believes an Exubera filing would ultimately help them (by reducing cynicism towards the notion of inhaled insulin), but they're not looking to file until 2010. At this point, they haven't yet completed an in-vivo safety study. They clearly want to partner this diabetes drug, and likely will spend little without one. Their tight relationship with Takeda may make them natural partners.

--By Stephen Simpson and Kelly Close

Appendix C: Obesity Timeline, 2004/U.S. Objects to WHO Plan to Halt Obesity

Obesity Timeline, 2004

1. **January 5: A study of 6,212 kids aged 4-19 published in Pediatrics by food guru David Ludwig** (who has done some excellent research pointing to the significance of the glycemic index) implies that every day, over 30% of U.S. children eat fast food, which translates roughly to six extra pounds per child per year. Consumption was highly prevalent across the US in both genders and all racial/ethnic groups. The study abstract notes that children who ate fast food, compared with those who did not, consumed more total energy, more energy per gram of food, more total fat, more total carbohydrate, more added sugars, more sugar-sweetened beverages, less fiber, less milk, and fewer fruits and non-starchy vegetables. Whew.
2. **Mid-January: The US officially objects to WHO's plan to halt obesity.** See below for our detailed, very negative, look at the US perspective.
3. **January 21: The CDC estimates that obesity cost the US $75 billion in 2002 in avoidable healthcare costs.** 64% of American adults are either overweight or obese as of 2002, up from 60% in 1990. An alarming 31% of the adult population is obese, up from 20% in 1990.
    a. Tangent on type 2 in kids: In Houston, as of 1995, more than 95 percent of all children's diabetes were type 1 cases. In 2003, the number of type 2 cases accounted for 31 percent of all childhood cases at the Texas Children's Hospital, said Dr. Siripoom McKay in a recent *Houston Chronicle* piece.
4. **February 24: The journal Surgery estimated there are 5,324,123 people, or 2.8% of the American population, who are eligible for obesity surgery.** "Of these … 38% rely on Medicare or Medicaid for their health insurance. Of the 28,590 gastric bypass operations performed in 2000, only 13% of patients used Medicare or Medicaid to pay for the operation. A significant fraction of the American population could potentially benefit from obesity surgery. However, many of those individuals are black, poorly educated, and impoverished. Public assistance programs need to account for these patients. Centers performing bariatric operations need to accommodate the educational and financial constraints these patients have when planning long-term postoperative care."
5. **March 2: McDonald's caves**, says it will cease supersizing. Hooray! Let's make this a national holiday. For perspective, keep in mind that the average Coca-Cola size in the 1950s was 6 oz, in contrast to today's super-sized 64-oz soda.
6. **March 10: The US House of Representatives** voted to ban lawsuits against the food industry for obesity claims, squashing the likelihood of class action lawsuits that contend food companies are responsible for increased obesity.
7. **March 10: No kidding, the *same* day, obesity expert Mokdad published in JAMA estimating 400,000 deaths from obesity in 2000, the #2 cause of death, just shy of tobacco's 435,000 level**. So guess which grew 9% and which grew 33% in just over a decade? Mokdad's persuasive piece calls for a more preventive orientation to healthcare in the US – stay tuned.
8. **March 11: So, I was positive this was a joke, but apparently not** – Krispy Kreme will offer a low-sugar donut "for dieters and diabetics." Note they didn't go into this on their March 10 webcast.
9. **March 12**: The FDA's overdue report on obesity "Calories Count" emerges, or as the website proudly announces, the agency's strategy is unveiled! More on our dim view in Appendix A.

-- By Kelly Close

U.S. Objects to WHO's Plan to Halt Obesity

In the face of a growing obesity and diabetes epidemic, the U.S. opposed the World Health Organization's strategy to halt and prevent the rise of obesity and diabetes worldwide. During a meeting earlier this year, the 32-nation executive board of the WHO released a preliminary report that called for two primary changes: 1) the food and beverage companies' reduction of fat, salt, and sugar content in their products, and 2) the restriction of food advertising aimed at children. Specifically, the WHO and the Food and Agriculture Organization recommends that no more than 10% of a person's daily caloric intake be from added sugars, fat intake should be limited to 15% - 30%, and saturated fats should make up less than 10%. Additionally, the WHO and FAO report recommends one hour of moderate exercise per day.

Though the WHO member nations plan to formally adopt the strategy in May, the U.S. objected, delaying the final version for at least another month by asking for more research. The U.S. questioned the scientific basis of linking fruit and vegetable consumption to decreased risk of diabetes and obesity, and argued that little research exists to support the recommended amount of exercise.

Several other countries, including Pakistan, South Korea, the Philippines, and Cuba, whose major industry is sugar, backed the U.S. position. The United Kingdom, Canada, and a number of European countries on the executive board opposed the U.S.

The Bush administration claims genuine doubts about the scientific validity of the council's recommendations and firm convictions that individuals remain responsible for obesity. However, many skeptics contend that the administration is more focused on ingratiating itself with the powerful sugar industry, which provides substantial campaign funding and votes in key election states, including Florida.

The protests of the U.S. have been criticized as a stalling tactic often used by food and beverage companies that call for more research to delay changes. Though the strategy would not be binding, many countries would use it as guideline for their own food policies. Other critiques of the U.S. cite the fact that the food and beverage industries are major political donors that could influence the next presidential election. Additionally, U.S. multinational companies whose major profits are from overseas may be threatened by a downward turn in marketing and sales of their foods.

The Health and Human Services and National Institutes of Health argue that the U.S. is trying to strengthen the WHO's strategy by making it more accurate in its recommendations and restrictions. Specifically, the NIH criticized the WHO report for not being specific enough by advising people to eat more fruits and vegetables in the place of less healthy foods, not just increasing consumption of fruits and vegetables.

Reports of the WHO on food and sugar consumption have been vehemently opposed by food and beverage companies in the past; though this time around, groups such as the Grocery Manufacturers of America whose members include Coca-Cola, PepsiCo, and Hershey, claim they support the fight against obesity. Yeah, right!

A conflict of interest? Florida Crystals Corporation's Jose "Pepe" Fanjul has raised at least $100,000 for Bush's presidential re-election campaign, J. Nelson Fairbanks, chief executive of US Sugar Corp, earned "Pioneer" status for raising at least $100,000 for Bush's 2000 campaign, and Cargill chief executive Warren Staley is a Pioneer for the 2004 campaign. In an election year, Bush is certain to win the favor of industry – and to keep the economy going at all costs, including health costs. In fact, Bush's conviction that high caloric intake will keep America's economy ablaze is most vividly demonstrated in a quote published in the Jan 31-Feb 6 2004 edition of *The Economist*: "*You [addressing David Gregory of NBC] get paid a lot of money; you ought to be buying some food here. It's part of how the economy grows. You've got plenty of money in your pocket, and when you spend it, it drives the economy forward. So what would you like to eat?"* Apparently, Bush equates the rate at which America stuffs its face with food with the growth of the US economy, ignoring the massive financial burden of obesity on the entire country – not only on the ill, but on the corporations whose workers miss more sick days and on the millions who shoulder the burden through rising health insurance costs.

According to HHS special assistant for international affairs William Steiger, who is representing the US at these WHO roundtables, Bush's chief objection involves the principle of shifting responsibility for the surge in obesity from an individual failure to exercise to recommending that government and industry assume a more proactive role in alleviating this great health burden. Alongside the US, Russia, India, and sugar-producing nations Mauritius and Grenada also oppose the WHO proposition. Although the WHO document does not mandate any direct government actions per se, public health workers believe the statement would greatly empower their efforts to recruit government action in the fight against obesity (for example, restricting advertising of junk food or taxing it).

The WHO proposal reflects the growing recognition that such chronic illnesses as diabetes and cardiovascular disease are no longer “luxuries” of the rich developed world. In fact, populations in developing regions may be at even greater risk from high-calorie diets and sedentary lifestyles because they carry “thrifty” genes that predispose them to gaining weight during times of high availability of food. The WHO’s scientific report drafted by 36 of the world’s experts in activity and nutrition warned that India would have one of the world’s highest rates of type 2 diabetes by the year 2025.

Having declared the fight against obesity one of his agency’s top national priorities, and even promising to slim down himself to lead the crusade, HHS Secretary Tommy S. Thompson now finds himself in a rather awkward position that has elicited wide criticism. For example, Bruce Silverglade of the Center for Science in the Public Interest, a Washington-based consumer group ripped, "*What we're surprised about is that Secretary Thompson, who has espoused so much concern about obesity, is privately working with representatives of the food industry to derail [this] initiative*." Professor Kaare R. Norum of the Institute for Nutrition Research at the University of Oslo, who chaired WHO scientific advisory panel, already has drafted a scathing letter to Thompson attacking the US position. Thompson seems to have been pressured by the food industry, the White House, as well as the Senate. Senators Larry Craig and John Breaux, co-chairmen of the Senate Sweetener Caucus, asked Thompson to instruct WHO to "*cease further promotion*" of the report. The food industry, through its powerful ties to the US Senate, even has threatened the WHO with withdrawal of the $416 million sum the US contributes to it each year.

The WHO votes on a final draft of the proposal when it reconvenes in May. In the meantime, the Bush administration’s contention that the WHO recommendations rest on shaky evidence certainly is bound to further fuel “diet wars” over what people should really eat and what role governments should play in protecting the public – and particularly children – from the influences of the food industry.

With at least 300 million adults clinically obese worldwide, the WHO continues to work on a final plan to be formally adopted by May.

-- By Martha Nelson, Janet Ng, and Kelly Close

Appendix D: Media Roundup

1. ***Improved Glucose Excursions Using an Implantable Real-Time Continuous Glucose Sensor in Adults With Type 1 Diabetes"***: DexCom's first peer-reviewed published results appear in the March *Diabetes Care*. The data clearly showed that continuous monitoring enabled more time spent in euglycemic range – music to the ears of patients with diabetes. Euglycemia is one of those novel concepts that most patients with diabetes would probably say they could never really fully achieve, certainly not with any consistency. Here's hoping that with TheraSense's Navigator already at the FDA, with Medtronic's Guardian 2 to be submitted shortly thereafter (they have promised by end of April), and with DexCom leading the implantable front, we're at the start of a new era. All the excitement aside – and I do think it's extremely exciting, as profound change in diabetes care could stem from this new technology – the FDA doesn't appear to be moving particularly quickly on any diabetes front these days (e.g., Detemir, Symlin, CozMonitor), and reimbursement (that black box…) always seems to take longer than it seems it ought to. (It's tough to prescribe unless it's reimbursed, but it won't be reimbursed until CMS sees a lot of experience with new products … circular?).

2. ***Editorial, The Need for Separate Performance Goals for Glucose Sensors in the Hypoglycemic, Normoglycemic, and Hyperglycemic Ranges***: This piece by Dr. David Klonoff is an important read for anyone following continuous monitoring. A companion piece to the DirecNet piece in the same issue of Diabetes Care, it makes the point that GlucoWatch and CGMS do not reliably detect hypoglycemia in kids and teens and that all monitors perform worst in the hypoglycemic range. Klonoff emphasizes that both episodic and continuous glucose monitors may detect hypoglycemia less accurately than many clinicians realize and that real-time continuous glucose monitor performance need to be closely scrutinized in the hypoglycemia range in particular.

3. **Super Size Me!** "Super Size Me," the buzzed-about Sundance prize-winning documentary (www.supersizeme) about filmmaker Morgan Spurlock's personal experience of the physical deterioration brought about by a month of consuming fast food three times a day. As a result of the "experiment", Spurlock gained 25 pounds over the month, while his total cholesterol level soared from 165 to 230. "Super Size Me"'s domestic theatrical and home video rights were recently sold to Roadside Attractions and Samuel Goldwyn Films, and the film is now set to hit nationwide theaters in May. At the 2004 Sundance Film Festival, the film earned Spurlock the documentary directing award for the way he pretty ingeniously juxtaposes the film's entertaining element with the dark, sobering results of his astonishingly rapid physical decline, which included vomiting, headaches, depression, and other signs of physical and mental deterioration.

   The inspiration for Spurlock's month-long, 20-city Super-size journey came from viewing a television clip in which two teenage girls were suing McDonald's for their obesity. This question of personal responsibility versus corporate responsibility represents a central issue in the film. Corporate deceit takes the brunt of the blame in the film, and the documentary's main shortcoming could be its rather reductive message that eating junk food is the sole cause of obesity. Another shortcoming could be the filmmaker's methodology: essentially any food eaten to excessive consumption could cause gastrointestinal problems. Thus, the main point of the film is not to condemn the fast food industry per se, but to criticize the way it markets itself for excessive consumption.

   Spurlock's message derives much of its potency from a clever use of images that juxtapose fast food's "happy" image against its grimmer reality. For example, Spurlock split-screens a smiley Ronald McDonald commercial against Curtis Mayfield singing his classic "Pusher Man." In another powerful image, he shows a colorful map of Manhattan with 83 flags crowded into the 14-mile island, each of which represents a McDonald's location. Truly horrifying. Spurlock also inserts vignettes of interviews with people on the street, the US surgeon general, and a fast-food industry lobbyist in between his gorging and vomiting.

So, look for "Super Size Me" appearing soon in theaters. But be prepared: you may not want to include an extra large butter popcorn and super-sized soda as part of your viewing pleasure! Instead, order a child's diet soda (16 ounces) or better yet, sneak in a bottle of water.

Before "Super Size Me" is released commercially, it will be shown at the San Francisco Film Festival April 24. We're buying a block of tickets so let me know if you will be in town and would like to come! The film will also be shown in Austin this Friday, March 19 (http://www.sxsw.com) and in Durham on April 3 (http://www.fullframefest.org/2004new_docs_list.cfm). Morgan Spurlock, by the way, sounds very cool. He was born in West Virginia and is a graduate of New York University's Tisch School of the Arts. He has written and directed shorts, music videos, and plays and this is his first feature film.

-- by Martha Nelson and Kelly Close

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