

The diet pill that will get you down...

Ascendiac[®]

A product of the Excella Pharmaceuticals Company

A Novel by Daniel D. Wambold, MD
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1.

The alarm woke her up, however Sharon kept her eyes shut as she groped for the snooze bar. Consciousness was fuzzy and indistinct, but even so, she was acutely aware of the date. The dry, unpleasant taste in her mouth reminded her that the third glass of wine last night wasn't enough to change the fact that today marked exactly half a year until her 29th birthday. She winced as she convinced herself that it really was March 10th. Ever since she had been a girl, turning thirty and still being single seemed like a life sentence to live alone. At some point, probably as a teenager, she decided that, allowing a year's engagement and additional time before that for dating and other necessities, she'd have to meet her husband-to-be by the time she was twenty-eight and a half. Although adulthood brought with it a realization that such concrete thinking was absurd, the haunting significance of the date day would not entirely fade.

Now, come on, Shar, don't get yourself worked up like this again. You're starting to sound like the woman in that movie, Bridget Jones's Diary. Thirty isn't even old any more. You've got a good job working for Dr. Sonders, and just because some guy hasn't magically appeared at your door doesn't mean anything. Hell, Alison Sonders herself has to be at least five years older than you and she's coping just fine. Sharon frowned and shook her head. *Of course, she's so thin and pretty that she doesn't have to worry about these things, does she...?*

The minutes ticked by on the snooze timer as she tried to minimize the impact of the morning, but just as she was at the cusp of figuring out her situation, the alarm rang again. She reluctantly slid her legs out from under the down comforter and planted her feet on the cold wood floor while switching on the radio for the morning news. As she walked over to the bathroom she wasn't even aware that she habitually averted her eyes from the dressing mirror so she wouldn't end up criticizing her body before she'd had a chance to shower and dress.

A mild ache pulled at her forehead— another remnant of last night’s excesses— so as the shower warmed up, Sharon found the bottle of Motrin on the top shelf of the medicine cabinet and shook two capsules from the container. She filled the glass by the sink and swallowed the pills, then drank more water to finish off the dry mouth attack. As she replaced the glass, the slightly ajar mirror showed her an unsolicited and somewhat unflattering profile of her midsection, made still less appealing by the harsh florescent lighting above the sink. She gasped slightly in surprise, then stated plainly to the mirror’s image, “That’s it, Sharon Keating, we’re getting you in shape. You’re not going down without a fight!”

As she showered, she began contemplating how she would accomplish this new goal. *Maybe I’ll join a gym because then I’ll have to go since I’m spending so much money each month. Then again, I thought that approach would be enough to convince me to use that stair climbing thing I bought that’s been neatly folded under the bed for at least a year. Power walking is supposed to be good for you, but March isn’t really a good month to plan to be outside every day. I guess I at least need to pick a diet, but which one actually works? Maybe I should send away for one of those fat burning pills the radio keeps advertising. I wonder if Dr. Sonders knows anything about that stuff. Well, whatever I do, this time I will stick to it.*

She continued washing, quickly massaging a handful of herbal shampoo through her shoulder-length brown hair while contemplating her new outlook, but an eerie sense of fate overcame her. After a moment of distracted preoccupation, she shuddered and decided it was most likely the result of having spent so many years of her life dreading the eventuality of this day.

2.

“Yes, what is it?” Dave Aswari didn’t like to be disturbed before 9 a.m. and Laura, his secretary, knew that any violation of this policy required a truly pressing issue. Dave personally credited his own swift ascension to manager of new drug development partly to his self-proclaimed near-genius intellect and partly to his compulsive scrutiny of each project’s daily progress. No detail was too small for his examination or, frequently, criticism. Whatever the real reason for his success, there was no denying that Excella Pharmaceuticals of Pearl River, New York, was in a position to begin reaping the rewards of his aggressive managerial skills. His weaker subordinates buckled under the stress of such supervision, but those who persevered found that each quarter’s bonus check grew quickly, as did the attendant stock options. Now, with two potential blockbuster drugs entering FDA Phase III clinical trials, Dave was in full stride, and even brief interruptions of his morning risked becoming serious flash points.

“Sir, I have Dr. Finnegan here. He says he needs to speak with you, and he says it’s urgent.” Laura held her breath as she held the phone, even though she really didn’t have reason to worry. Jack Finnegan was the lead medical investigator for Ascendiac, the diet pill that Dave projected would propel Excella to the ranks of Merck and Pfizer. Although he struck Dave as being a little out of touch with the business side of selling pharmaceuticals, Jack certainly was a brilliant researcher. Occasionally the two found themselves at odds, usually over issues that Jack termed “Proper Scientific Techniques,” which would clash with what Dave considered to be sound business principles. To Jack’s chagrin, dollars and rank usually took precedence in the end, though resolution of these conflicts was rarely unilateral. For his part, Jack was careful to pick his battles and his terms for concession.

“I see,” Dave answered Laura in a slightly annoyed tone. “Well, OK, send him in, then.” As he hung up the phone he moved a few extra papers and folders onto the center of his desk to make it absolutely clear that he was being interrupted by Jack’s unscheduled visit. This display, however, was superfluous since Dave possessed the uncanny ability to telegraph exactly the emotions he wanted to convey solely through his body language. Alone, the dark eyebrows over his Mediterranean complexion could speak volumes across a conference room, and added to his six foot tall frame and dark brown, razor-sharp eyes, he could intimidate or charm with the charisma of a king.

In truth, the effort Dave was currently making to appear busy was much more an unconscious admission that Jack’s continued cooperation with the Ascendiac project was vital to the success of Excella. Although he never fully understood why he felt slightly threatened around Jack, the unease stemmed from Dave’s fierce sense of independence which clashed with the occasional and unavoidable need to rely on others. He was used to absolute power over projects, but in the realm of the drug industry, Jack held certain crucial cards, especially when it came to a working knowledge of the biology behind the pharmaceuticals in development.

Dave’s background was now firmly entrenched in the business aspect of medicine, having graduated fourth in his class from Columbia Business School in 1993, though the route had been indirect. A decade earlier, his undergraduate years at Penn State were split between football games, parties, and achieving a 3.6 grade point average for his combined English and economics majors. He considered it an accomplishment at the time to have taken the absolute minimum number of credits in science courses, though now he often wondered if he should have taken that subject more seriously. As a freshman, he had even leveraged his charm with the dean

of students to garner credit towards Penn State's core requirements for a high school advanced placement class in chemistry which he had barely struggled through.

With two degrees and the drive to succeed, Dave moved to Philadelphia after college to take a job with a financial firm called Cavanaugh, Wilson, and Wu. He was brought on as a stock analyst for their medical devices division, enduring a crash course in the minutiae of health care financing. Each company's evaluation showed him a new facet in the business of health care, ranging from predicted market placement to varied patient populations to the gamut of insurance and government-financed reimbursement. Making money in this field required not only a successful product, but a demand for it and someone willing to pay the ever rising costs. Losses could be swift and blinding, especially when other companies trumped a clinical accomplishment with their own technological advances and innovations. Long term investments had to be restricted to large, multidisciplinary companies which could effectively protect their products through both solid monopolies and relentless scientific progress. As it was, CW&W's focus was largely on turning quick profits, so Dave learned early to dart in and out of positions before the luster had disappeared from the newest medical miracle.

During the late 1980's, with black Monday still weighing heavily on investors' minds, profits were hard-earned by the few analysts lucky enough to stay out of the red ink. The SEC was keeping a particularly close eye on transactions because, especially in difficult times, insider trading and illegal deal-making flourished. Many good people ruined their reputations and their livelihoods by succumbing to the allure of fast money, only to find that they had been ferreted out by the SEC's rapidly expanding application of computer algorithms to identify suspect trades. Although he watched as two colleagues were convicted of securities fraud, Dave himself had never betrayed his belief that business was built on a set of rules that applied to everyone.

That's not to say that he didn't feel it was his duty to make every effort to use the rules to his advantage, but he still saw a clear line between manipulating the law and breaking it.

Dave prospered during those years despite a stagnant market. His efforts were rewarded with promotions and bonuses, though he always considered true success to lie further up in the chain of command. So, in 1990, with just over \$80,000 in cash and liquid assets, he applied to business school. His unblemished record and glowing references secured him a spot at Columbia's Business School for the 1991 academic year, but despite his rationalization that it was better to study in New York than Philadelphia, he tacitly resented the fact that Wharton had turned him down. To prepare for the transition back to academia, he resigned from CW&W three months before the school's September start date to enjoy some of the fruits of his labors by travelling around Europe. For part of the time he rented a 36' sailboat complete with a two-man Spanish crew. He learned to sail (and he polished his Spanish) while exploring the pockets of culture in the port towns along the coast of Spain and Portugal. A picture of the boat and crew still hung proudly on the wall behind his desk as a constant reminder of the simple beauty and danger embodied in the strength of the ocean.

Jack entered the office and strode purposefully up to Dave's desk, carefully ignoring the attempt Dave was making to appear too busy to be bothered. In comparison, Jack's 5' 7", 155 pound stature failed to carry the conviction of Dave's imposing presence. His fair Irish complexion and light auburn hair fit the stereotype of a hard-working scientist much better than the tall, dark, and handsome look possessed by his superior. Nevertheless, there was a sharp, analytical edge behind Jack's bespectacled face which was always evaluating not only the next stage of a conversation, but the one following that, too. It was akin to the deep insight that chess masters possess which allows them to see the consequences of moves that have not yet been

made, but which could be rendered harmless if the right position were taken at that exact moment. Jack decided to let Dave finish his paper charade before beginning, so he stood at the desk quietly, until Dave looked up and acknowledged him.

“Jack, good to see you. Have a seat. What’s on your mind?” Although the greeting sounded cordial, Dave’s eyes told a different story.

“Well, I figured you might already know the answer to that question. I got a copy of the Phase III protocol for Ascendiac this morning and it seems that the changes we discussed last month hadn’t been implemented.”

Dave cleared his throat briefly, knowing full well what Jack was referring to. “Yes, I’m aware of the parameters of the trial, but you need to understand that the FDA has approved our protocol as it is. If they don’t think there’s a need for us to collect data outside of the study timeline, then I’m satisfied that we’re doing our job here.”

“Well, did you specifically *ask* them if they thought that a two week crossover tail was a good idea or did you just decide that, if they didn’t complain, it must be the right thing?”

Dave’s eyebrows lowered a bit, preparing for combat. “Now come on, Jack, you know how these things work. As soon as you start suggesting to them that there might be something to worry about, they’ll triple the requirements for approval. Besides, I’ve had someone from regulatory looking into the precedent for drug withdrawal studies and they’re almost uniformly unnecessary after Phase II.”

“Yeah, I know that. I’m also aware that our Phase II data are completely clean, but I really need you to understand that dose range studies don’t accurately address the potential changes that receptor-modifying drugs like Ascendiac can cause. Just knowing that a few doses doesn’t lead to withdrawal symptoms really won’t uncover potential problems that can occur

with longer-term use. I'm just not sure I see the reason to pass up the opportunity to collect some more information about the drug.”

Dave shrugged dismissively. “It’s just as I said during the final multidisciplinary meeting when you brought up the same issue. First of all, it’s an expense that can’t be justified because the FDA isn’t asking us to look at patients several weeks after they’ve completed their trial. Trying to acquire those data points would just complicate the study as more people dropped out for the usual reasons. I mean, it’s hard enough to keep tabs on a few hundred people over the course of two weeks, much less a month or more. How many are expected to be lost to follow-up each week of a study? Something like three to five percent, right? That adds up to a lot of unknowns after an additional month, with each question mark waving a little red flag to Andy Rheinberg and his whole FDA review board. Second, since it’s not customary to acquire that information, the fact that we’d take an approved protocol and try to modify it to make it *more* stringent would cause Andy to crawl up our ass with a microscope. Most importantly, Jack, what do you really think we’ll find? That they get fat again? I mean, we’re marketing an appetite reducer, not a miracle drug. As soon as they’re off this stuff, how many are going to stick to some low-calorie diet and exercise routine? Now, I know you’ve told me that this drug is different— that it’s not a stimulant like Fen-Phen— but you don’t really think it’s going to change peoples life-long overeating habits, do you?” His expression made it clear that this was strictly a rhetorical question.

Jack paused for a moment, trying to choose the most effective tack from the multitude of objections Dave raised. He savored the opportunity to single one out, eventually deciding to focus on the issues relating to Dave’s attempt to understand the physiology of the drug. Treading carefully to avoid insulting him, he nodded thoughtfully and raised his hand. “When you put

patients on blood pressure drugs like ACE inhibitors, their pressure definitely drops. When you stop those drugs, the blood pressure climbs back up. That's how some drugs work. However – and I suppose I haven't really made this part clear before, so bear with me for a minute– when you put people on other blood pressure drugs like beta blockers, their pressure also drops, but if you then stop the drug, the pressure increases *beyond* what it started at. It takes a few *more* days for it to normalize again, and during that withdrawal time, patients are at an increased risk for all sorts of problems like heart attacks and strokes.”

Dave threw up his hands. “But that's the same point you made the other day! I and the FDA have accepted the fact that there could be a rebound – that is the word you used, right?– a rebound increase in the appetite. Even if it happens, and I think we both have to agree that we really don't have any reason to believe it will, it's probably going to look just like a dieter stopping their diet. There's always a period when they overdo it, then they settle back to their normal eating level. Honestly, I still can't comprehend why you're so concerned about this.”

Jack already had him wandering down a primrose path towards the trap. In as non-condescending a tone as he could manage, he responded, “You're right insofar as a little overeating probably won't hurt the patients, but what if they continue for several days? I don't think we want to get a drug approved that results in patients *gaining* weight after they stop using it. Just like with the beta blockers, sometimes a little increase is harmless, but other times, it can cause real and very embarrassing problems. I doubt a brief stint of gluttony could lead to serious health concerns, but I just think we're swimming in uncharted waters here, and we could stand to be a little more cautious until we understand the drug better.”

Dave realized that he was clearly out of his league arguing about the potential medical aspects of the drug. He decided it might be prudent to throw Jack a bone on this one without

actually conceding to changing the approved protocol. He raised his eyebrows invitingly. “Look, what sort of a compromise do you think we could make on this? Is there something I can arrange internally for you so that you can get this information without making it part of the study? I could offer you a few people so you can have them phone your study patients a couple weeks after they’re done just to check in on them. You know, spin it as sort of a courtesy thing. ‘Our company cares.... How are you doing?’”

“I considered that approach, but I think we need to make it a little less suspicious. No one believes that companies actually *care* about them; That’s more of an advertising angle. I had a different concept, but it will cost us a small amount of money.” The last phrase caught Dave’s attention and he frowned incredulously but held his tongue. “How about a week after they’re done with the study we send a \$10 coupon for one of our products, like a bottle of multivitamins, along with a market survey that’s part of the mailing. We could include a detailed section on diet aids and finish with a section on the patient’s current physical status. Anyone who didn’t respond could get a follow-up call about the survey. That might help keep things low-key.”

Dave ran the numbers in his head briefly before deciding that a \$10 coupon would cost next to nothing given their huge markup on vitamins. He decided it seemed like a pretty innocuous idea which might even prove useful if the data showed the weight that patients lost stayed off for more than a week. Without wanting to sound as though he’d given in, he sighed. “Well, I guess it could be worse. You could have asked for a \$20 coupon! All right. I don’t think I could easily justify the expense to our shareholders, but then again, we just might find that your little miracle pill actually works better than you expect, which would give us a nice marketing angle. Send me a memo.... No, actually, *don’t* send me a memo. I think we should keep this discussion between us for now so that there’s nothing for the FDA to bite on if they decide to

subject us to one of their audits. We can just give the list of study subjects to the marketing people and I'll have their director suggest they organize your survey. OK?" His eyes plainly said that the discussion was over.

"Yeah, that's great. I mean, I'd have liked to have done this the right way, as part of the Phase III study, but despite what you think of me, I also really want this drug to fly. This thing's been my baby for almost two years now, and it will certainly mean great things for Excella and for us personally if it gets a green light. Thanks for your time, Dave. I know you're busy at this hour." He motioned towards the artificially cluttered desk. "Let's just hope this drug does for people what it did for the monkeys." Jack stood and walked to the door.

Dave, slipping back into his charismatic leader role, joked, "Hey, lots of people make *one* blockbuster drug. The *real elite* come up with two!" As the door shut behind Jack, Dave's smile disappeared nearly instantly. *That agreement's fine, Jack, as long as everyone does well when they come off of your drug. I don't know how far I can trust you, though, if you start worrying about some imagined problem with the follow-up patients. I suppose I'll need some sort of contingency plan if you threaten the success of this project with your little survey stunt.*

Dave's mind began to wander through the list of possible responses to that eventuality.

3.

Alison Sonders looked over her schedule for the day, shaking her head while she wondered how she was going to manage to see eleven patients. A few of them were thirty minute follow-up visits, but the majority were full one hour sessions which, even in the best case, would each require an extra fifteen minutes worth of paperwork. She checked her watch to find she had almost ten free minutes before her first appointment, so she took another sip of her morning coffee and leaned back in her leather chair, allowing a small portion of her blonde hair to fall in front of her face. She closed her eyes briefly and vaguely wondered how this girl from a quiet town in New Jersey had managed to graduate from Dartmouth medical school and build one of the busiest psychiatry practices in Manhattan. While random thoughts fought for attention in her still caffeine-deprived mind, a seemingly disconnected memory from her childhood caught her by surprise.

It was late November, and she was at her eighth birthday party, sitting at her parents' kitchen table with her four girlfriends. She could see their faces so clearly that the party might as well have been this morning. Betsy Staub, with her curly red hair and freckles was to her left, then Liz Whitestone, the girl whose mother was divorced. Liz always struck Alison as being just a little too outgoing most of the time, except on the days before she was going to visit her father for the weekend. Those days, she was generally quiet, almost sullen. The fact that she lived just a block away made her an appealing friend, though, so her moods were generally forgiven. Across from her was Jenny Thompson who moved out of town six months later, and finally Tammy Hereford, Alison's best friend that year. Tammy and Alison took dance lessons together after school and they spent countless hours each week talking about how they were going to grow up to be ballerinas who would dance in big, exciting cities around the world.

For gifts, the other girls had given Alison toys which were thoughtful but uninspired. Tammy's present was the last one Alison opened, and she smiled at her friend when she realized the box didn't feel like it contained another doll. The smooth wrapping paper slid under her fingers as she ran her hand along the side of the box, the excitement building every moment as the decorative covering reluctantly yielded to her effort. The box contained within was white with an unmistakable red 'B' on the top, the trademark for the Brandtley Fashions store in New York, twenty-two miles away. Although Alison had never been to the store, their newspaper ads, always featuring attractive models wearing the latest Paris and New York styles, had caught her eye a year earlier. She had decided that any girl lucky enough to wear such beautiful clothes must feel just like a princess.

Her eyes grew wide and she turned to Tammy with a look that asked, "*Is this for real?*" Tammy smiled broadly and nodded.

"Oh my gosh!" Alison squeaked as her now-trembling hands worked to open the box. Inside lay a soft, baby blue sweater with fuzzy cuffs and sequins sewn on in snowflake patterns. "*It's beautiful!*" She pulled the gift from the box and held it up to her shoulders. The sleeves were cut just a little short to show off the owner's wrists, and the waist was tapered in gently to give a feminine shape without being overly revealing.

Beth Sonders, Alison's mother, who had been watching quietly from the doorway, walked into the room to get a better look at the gift. "Wow, Tammy," she said, "it's really beautiful. Did you pick it out yourself?"

"Yes, Mrs. Sonders. My daddy works in Manhattan and he took me to the store. He asked the man there where the young *ladies* clothes were." Tammy savored the word 'ladies,' because she knew that, at eight, all girls became young ladies, and ladies never bought girls' clothes.

Tammy had explained this to her father during the car ride to the store, making it clear that, in five and a half weeks, when *she* turned eight, the same rules would apply to her. “We looked at every rack and finally I found this sweater. My dad said it was really pretty, too.”

Alison was still completely consumed with this treasure and she was stroking the soft fabric as she held it against her shirt. “It’s so soft! I love it, Tam!”

“Why don’t you try it on, sweetheart?” Alison’s mother suggested, motioning towards her bedroom on the second floor. Alison ran off and returned a few moments later, feeling like she could walk on air. The sweater fit perfectly, and as she walked into the kitchen she imitated the deliberate, accentuated strides of a runway model, complete with a pirouette before retreating to the doorway again. Even her father, who had entered the room, was surprised at how mature his daughter suddenly appeared.

“Hey, is that my little girl?” he quipped, only half-kidding, but mostly wondering to himself how time had managed to pass so quickly.

“Dad, I told you! I’m a *lady* now!” She smiled broadly at him as she shook her finger in his direction.

“Oops! I forgot. Well, how would a *lady* like a present from me and your mom? It’s not a Brandtley present, but I hope you’ll at least *make believe* you like it, too.” He produced a small box the size of a paperback book which was wrapped in pink and gold paper. There was a large bow in the center which covered almost the entire top of the box. “Happy birthday, Alison.” He kissed her forehead as he gave her the box.

Alison tore the paper off to find a plain blue box inside. There were no tell-tale markings decorating this one, so she opened it. Inside was a white envelope, also bereft of print or designs. The thrill of Tammy’s gift overshadowed the suspense of this embedded present, but when she

finally reached the contents of the envelope, she found three tickets clipped together in the middle. The words “Nutcracker Suite” were printed prominently across the top, with the show date of December 18th stamped below. The performance was to be at the Metropolitan Opera House at Lincoln Center in New York City, one of Ballet’s most prestigious venues. Certain this was too good to be true, Alison read and re-read the ticket, her voice bubbling with uncontrollable excitement.

“Oh, Daddy, *thank you!* This is the best present I’ve ever gotten! I can’t believe we’re going to see real ballerinas! I heard they practice for eight hours every day to be good enough to perform there and they are so beautiful and graceful that they look like they’re angels floating across the stage!”

“Well, sweetheart, that may be true, but you know that you are *my* angel, and that’s why your mom and I wanted to take you to see this show. Happy birthday, Alison.”

“I love you,” she said as she buried her face in his midriff and gave him a hug. After a moment, she looked up, feeling guilty for lavishing all her affection on her father. “I love you, too, Mom,” she said as she proceeded to hug her as well, though she was truly daddy’s little woman at heart. “Hey... Can I wear the sweater Tammy gave me to the ballet? Then it would be like Tammy was there with me, too!”

Her mother smiled. “Sure, Al, that would be just fine.”

The distant sound of the office’s outer door closing snapped Alison back to the present. She blinked briefly as her medical mind began to process the memory, dissecting the feelings and relationships within. Years of complete devotion to psychiatry made this an inexorable and routine exercise in virtually every segment of her life. Talking with friends or family, or even introspecting into her own psyche would prod her professional skills into action. While such

mental investigations were only occasionally counterproductive, sometimes she felt like her internal clinical monologue would interfere with her firsthand emotional responses. Although there was a lingering sense that this unexpected recollection of her eighth birthday might have a deeper meaning for her, Alison pushed further consideration of it to the background in favor of focusing on her morning work.

She opened the top chart on the stack, reminding herself that her first patient was a new referral named Charlotte Jonitaur who had been treated for depression for five weeks by a primary care physician, known in medical circles as the PCP. Apparently, the progress was less than expected on the first-line medication which the PCP had chosen, so Charlotte was referred to her for further evaluation and treatment. Alison rose, pushing the last bits of the birthday memory out of her mind, opened her door and nodded to Pearlene, the office receptionist, indicating that she would see her first patient now.