JONATHAN

by Michael Sykes

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"Honey, it's for you..." Alan woke, squinting into the light from the bedside lamp. After a moment, his eyes adjusted enough that he could make out the shape of his wife leaning over, thrusting the phone towards him. "It's your mother."

"Dammit, can't she-" he started, but a brief look from Laura silenced him. The subject of his mother's inability to comprehend the concept of timezones was nothing new to their marriage. It was mornings like this that he rued the day he had ever accepted a position on the west coast. A quick glance at the alarm clock revealed it was 5:30 am. Early, but he'd never get back to sleep. Oh well, he had a lot of work to do today anyways.

One hour later he pulled into the parking lot outside of the Fairchild Building. He had come to Stanford 3 years ago to escape the more formal confines of the East Coast for the casual California lifestyle, or should he say the confines of his father. His mother had disapproved, mostly because she had enjoyed the freedom to stop in on him and his wife unexpectedly while they were in Boston, but his father and he agreed it was a wise decision. Ten years ago his father, a senior Professor at Harvard, had won the Nobel Prize in Chemistry. Many people questioned Alan's decision to enter the sciences at all, it wasn't easy to fill shoes that big, but given that the decision had been made there was an unspoken agreement with his father that they ought to at the very least put some distance between them. There weren't that many cars in the parking lot at this hour, at least not that many that he recognized. Being right beside the medical school had it's advantages, but it also meant competing for parking with the doctors and medical students who worked all hours. He knew he'd be alone once he got inside.

"Dr. Simpson?" Alan hated it when people called him that. Summer students were the worst. "Come in..." Usually he left his door open, but it was grant time again, and he was searching for some peace and quiet. He couldn't understand why Sheryl insisted on coming in so early in the morning, it was still before 8, but evidently she felt it justified her early departures in the afternoons. "I hate to bother you, but I think you should take a look at this..."

Sheryl was an especially promising young scientist, and was working in the lab for most of the summer before leaving for Europe for two weeks. A newly graduated Stanford Alumna, she would be doing her graduate work at the Scripps Research Institute in La Jolla, and Alan felt himself increasingly disappointed in this arrangement as the weeks wore on. He wished that she would come to work for him, but the lure of a fiancé in San Diego was too great of an incentive. Sheryl had initially started her work alongside Maria, a young Colombian Post-Doc of Alan's who had moved to the United States after high school to attend Harvard as an undergraduate. Alan had always wondered how she could have afforded the move, but he felt that his suspicions were best kept to himself. By July though, Sheryl had proven that she was more than capable of working on her own. She had been studying Lectin and its effects on human obesity. In mice, defects in Lectin, Lectin production and Lectin receptors have all been shown to result in obese phenotypes. In humans however obesity was related to blood Lectin levels, and the Lectin and Lectin receptors themselves remained unchanged. Alan's group, with Sheryl and Maria in particular, had been actively searching for new causes of human obesity.

Sheryl had collected pancreas samples from a number of obese patients who had died before the age of 50 at the Stanford Medical Center. A protocol was relatively well known to isolate the Lectin receptors from the pancreatic tissue, and these could be reconstituted into model membrane systems. However, the relatively low quantities of Lectin receptors available via this method, as well as the low number of donor pancreases, had hampered research in the field. Realizing the need for high sensitivity techniques Sheryl had turned her attention to FRET, Fluorescence Resonance Energy Transfer. Taking advantage of two cysteine residues located on the surface of the Lectin receptor, she was able to modify the receptors with two chromophores to perform the FRET measurements. There was some concern that the modifications would adversely influence the integration of the receptor into the membrane, but as it turned out the system worked perfectly.

"Look at this" Sheryl exclaimed, directing Alan's attention to a series of spectra she had

displayed on the computer screen. None of it made sense to Alan; he had heard of FRET before but he had left the specifics entirely up to Sheryl and Maria. Trained in molecular biology, he had avoided chemistry courses whenever he could. "I've managed to obtain samples from 15 different patients this summer" she continued, "and the results have always been the same. Helices A and E are about 20 Angstroms from each other in every case. This is what we might have expected, and I was about to give up on the measurements, but look at this last one; I just obtained the sample last week." She ignored the relatively blank stare given by her supervisor; did he really need to wonder why she wasn't continuing on in his lab for graduate school? Maria had always said he was a second rate scientist compared to his father. "This clearly indicates that the two chromophores are now 25 Angstroms apart." She continued on, "This is a huge difference, and clearly within the realm of statistical significance. Something big is going on here..." Alan's blank stare slowly turned into a smile, and it was all he could do to resist hugging her. He would always remember the pain that a false accusation of sexual harassment by an embittered undergraduate had caused his father years ago. "Fantastic!" he exclaimed instead, "and just in time. This is certainly a nice way to wrap up your summer." "Now I've only done this measurement once," Sheryl cautioned, "and it will have to be repeated twice more to be consistent with all the others, but that should just be a formality." Sheryl had enjoyed her summer, but she was ready for a vacation, and even as she finished her sentence her mind drifted thousands of miles away. Her fiancé and the French Riviera beckoned, and she had decided days ago that this measurement would be the last one she would take before Grad School, no matter what the result. That afternoon Sheryl said her good-byes and left the Simpson Lab. Sheryl wasn't the only one not paying complete attention. Even as she finished, Alan was already on his way back to his office to revise his grant application. This was just what he needed to assure the renewal.

This was Alan's first grant renewal application since he had arrived at Stanford as an Assistant Professor, and he knew that he needed to be aggressive. He didn't have to make any large changes, but there was the auspicious addition of a single line in the text:

We have furthermore obtained conclusive evidence that there is indeed a form of Lectin related human obesity that stems not from a defect in the Lectin signaling pathways as has previously been the norm, but rather from problems related to the human pancreatic Lectin receptor.

He breathed an audible sigh of relief as he completed the form. He wasn't concerned that the evidence was not conclusive yet, what had Sheryl said, it was a formality, and best to keep the method secret for now. He couldn't afford to let that get out.

"So this is the new lab?" Alan's father had never visited him at Stanford before, but having been brought here as a Guest Lecturer to the Chemistry Department he had stayed on a couple of extra days to visit. The elder Dr. Simpson, and rest assured that was how he preferred to be addressed, was still an imposing figure though into his 60's. He also remained as sharp and as bright as ever, and even the Nobel hadn't managed to sway him from an untiring research program. He was a man determined not to hit the career downslope that so many professors reached and had long ago vowed to retire the instant he no longer felt he was making a significant contribution to science. It wasn't clear if he would ever reach that point. An organic chemist by trade, Dr. Simpson had in more recent years turned his attention to metalloproteins. Using his vast knowledge of synthetic methods he coached his group through the design of novel ligands that could be used to probe the metal binding sites of proteins, and employed a wide range of spectroscopic techniques to study them. He was thrilled at his son's latest results. "These are the FRET results dad" Alan indicated, much more confident now in his understanding of the technique. Since Sheryl's departure, he had taken it upon himself to learn the methods behind her research. He also didn't want to embarrass himself in front of a Nobel Laureate, even his father. "You know Alan, a Postdoctoral fellow of mine has been working on a new spectroscopic

technique in the lab that I think would be well suited to this problem." His father paused, and Alan's mind began to race. He and his father had often toyed with the idea of collaboration, and he had often sought his father's advice on a variety of scientific problems, but he did not recall his father ever offering such unsolicited aid. "In addition to my recent studies on metalloproteins, we've also become interested in membrane proteins." His father continued, not letting on if he noticed a change in Alan's demeanor. This was news to Alan. "We've yet to publish any work, but George has been working very hard to develop some new Xray diffraction techniques that should work perfectly here. As you might know, there have been recent advances in the field of NMR that rely on the partial orientation of samples by the magnetic field. This sample specifically orients with the direction of the magnetic field, and this results in residual dipolar couplings that are not normally observed, and distance information over longer ranges than NOE's." Alan was familiar with the concept, but he had yet to see the connection. And while he knew what an NOE was, dipolar couplings sounded like a personality disorder. His father continued, "By reconstituting the Lectin receptor into the appropriate lipids, we could orient the entire thing in a magnetic field. Two perpendicular magnetic fields would allow us to restrict the lipid bicelles to a plane. This would essentially create a two-dimensional lattice, but unfortunately there remains a rotational degree of freedom for the receptor in the membrane. However, if we engineer in paramagnetic ion binding sites onto the two cysteine groups which you've mentioned, the receptor just might then orient specifically in the membrane, creating a three-dimensional lattice. The paramagnetic ions have the added advantage of being heavy atoms, which will scatter well in the Xray beam. This will allow us to work with the relatively low sample quantities which you have to produce accurate results." Alan was stunned. He knew that his father was a brilliant man, perhaps even a genius, but to come up with that on the spot was simply incredible.

The two sat in discussion for several minutes, and Alan consented to give some of his precious sample to his father for the experiments. He was the only man Alan would have trusted at such a time, and the prospect of collaboration excited him more than he cared to admit. He had

always been close to his mother, but his father had always played the role of impenetrable scientist well; even at home. Alan had gone into science to please his father, but he sometimes wondered if he ever would.

There was rarely a party in either Simpson lab, but the younger scientist decided to make a special exception today. As expected, on the strength of several respectable papers and the promise of Sheryl's results, Alan's grant had been renewed. He hadn't yet followed up on Sheryl's initial measurements, but he was not concerned. Tomorrow he would discuss it with Maria.

"I'd like to talk to you about some of the work you and Sheryl did this summer Maria, hopefully sometime today," Alan ventured early the next morning. "Alright, but I don't know how much I have to say" she replied. By now the entire lab knew of Sheryl's results, though even they were not sure how she had obtained them as Alan had yet to really discuss any of it in detail. "What do you mean?" "Well," she replied, "Sheryl pretty much did things on her own. I mean I was involved with a lot of her earlier work, isolating the receptors and reconstituting them into the membranes, but you know all about that. The FRET stuff was all her's though." The smile suddenly disappeared from Alan's face, and he slowly began to grow worried. "I'm sorry Maria, but I don't think I follow. I thought that the two of you were working together?" "We were, but you know as well as I that Sheryl didn't need me around." Maria replied, growing somewhat annoyed. "I'm a molecular biologist, not a spectroscopist, so I didn't really have anything to add to her fluorescence measurements. She kept me up to date on her results, but that's about it."

The reply to his email was immediate, and punctuated with a loud 'Beep!';

"+ 7 Dec 30 Mail Delivery Subs (1,879) Returned mail: User unknown"

What the hell? Alan was positively confused. Sheryl had given him this address shortly before

she left for France, and had assured him it would be operational in September. Having found out from Maria several days ago that Sheryl was the only one in the lab who knew about the FRET measurements, he had decided to email her. It had taken a call from an old friend of his to stir him into action though. Jeffrey Simons, a colleague of his from Yale had politely inquired about when he was going to publish his results concerning the Lectin receptor. Evidently he was quite excited about it, as were several other individuals. Word had gotten out. Alan picked up the phone, struggling to recall the Area Code for La Jolla.

"What's wrong dear?" His wife could tell within seconds when something was wrong. It was one of her abilities, like his father's ability to make any accomplishment seem small in comparison to a Nobel prize. He decided he had to tell her something. "You remember that summer student of mine, Sheryl Garcia?" "Of course, wasn't she the one that you wanted to work for you?" "Yes," he continued, collapsing into a chair. He sat, just staring for what seemed like minutes on end. "Well?" Laura was not about to quit. "She never came back from Europe." The confusion was evident on Laura's face. Why would he care so much about that? He wasn't having an affair with her, was he? She was snapped out of her reverie by her husband "It's just that I need her help to complete some very important work..." "Well don't worry" Laura assured him, "I'm sure you can figure it out on your own."

That's what Alan had thought too, and Maria, but between the two of them they had managed to waste almost all of the rest of their sample. And the chances of another patient showing up with the same condition were remote at best, at least in the near future. "Sheryl just had a magic touch with the equipment" Maria once told him, "she was just so confident, like she grew up in a lab." As it turned out, that might as well have been the truth. Sheryl's mother had died at a young age, and her father had raised her alone. Working for IBM he had often brought her into the laser labs at night, where she would do her homework or watch him at work. That might also be why, the August before she was to begin her graduate studies, she burnt out. Sheryl figured that a year backpacking through Europe and Asia might help her get back on track, and the

people at Scripps had no problem deferring her admission for a year.

"Hi Dad.." He was cut off by the sound of his father's voice. "Alan, I was just about to send you an email, George has had some excellent results." "Well that's exactly what I'm calling about" the younger Simpson continued, "We've been having some problems." "What do you mean by problems?" his father continued, "I thought that you had all of the results that you needed?" "Not really" Alan mumbled, feeling like a child again. "It turns out we've been unable to repeat any of the measurements without my star student, and if it's not too much trouble I was wondering if I could have back what's left of the sample I gave you." "I'm sorry Alan, but I don't think that's possible." "Why not" Alan asked, as a shiver descended down his spine. "It's all gone." There was a long pause. "Dad, I need your help..."

A few short days later Alan sighed as he completed the last line on the manuscript. He had just finished writing up a manuscript with the following title:

'Studies on a New Form of Human Obesity by a Novel Spectroscopic Technique.'

Two names appeared at the top; 'Alan Simpson and Maria Gonzalez.' They were the only two still in the lab on that Saturday night, and besides them only Dr. Simpson and his postdoc George would have noticed anything wrong with the authorship. George however had departed for his native Greece a week earlier, recalled for an indefinite amount of time by family tragedy. The other three were not about to let on. "Jonathan really came through for us this time," Maria murmured. "What?" Alan replied, his eyes narrowing ever so slightly. "I said that Dr. Simpson really came through for us" Maria repeated, but Alan was not even listening to her. Nobody ever called his father Jonathan.

"Hi Mom, it's Alan" "Alan sweetheart, how are you doing, I'm so glad you called!" He

didn't understand why his mother still insisted on calling him sweetheart, but he supposed he didn't mind. "You never call, is everything okay?" It was true, he never called his mother; she phoned him so often he had never felt the need to. But everything was not okay, and he needed someone to talk to. "I thought you would be with your father" she continued, barely even pausing to let him reply "I wanted to phone you myself but I hate disturbing the two of you." "Father?" Alan queried, surprised at the statement. "Yes dear, your father, hasn't he arrived yet? He's gone to see you so many times these last three years I hardly think anything of it anymore, but I imagined the two of you would be off having dinner or talking about your science or whatever it is you two talk about." Alan just sat silently, while his mind worked in the background. "Alan? Honey?" "Mother, I have to go"

"Sally, I'm concerned about him" Laura pleaded, "I just don't know what to do." Laura's sister had come over to comfort her. Alan had not left the house in four days, refusing to go to work. He had barely eaten, and mostly sat in his room, thumbing through old family photos. "He hardly eats, he won't talk to me, and he certainly won't tell me what's wrong." She sighed heavily, as Sally put her arm around her. Neither of them noticed Alan walk out the door and get in the car.

"Dad, this is Alan." "Hi son, how are you?" his father asked, idly thumbing through the latest issue of 'C&E News.' Alan looked carefully at the manuscript in front of him, for what might have been the 1000th time, and then again at the picture of his mother. "Dad, I know about you and Maria." It all made sense, the perfect alibi. A son on the west coast to visit, and a wife who was so happy that her husband and son were spending time together that she would not even dare bother Alan with her traditional phone call. "I'm going to tell mother." a long pause followed, and Alan could almost feel the weight of his father's presence on the other end of the line. Strangely, his father's voice remained calm, or was it simply cold. "Alan?" he asked, "do you know what I have in front of me?"