

## A conversation with Jeffrey M. Friedman

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### Conversations with Giants in Medicine

We are joined by Jeffrey M. Friedman of the Rockefeller University, a scientist who has been at the center of discovery of the molecular determinants of why we eat what we eat, and more specifically, why we eat so much of what we eat. Friedman (Figure 1) has spent his research career on the discovery and characterization of leptin, a key hormone regulating appetite and hunger. The full interview can be seen on the JCI website at <http://www.jci.org/kiosk/cgm>. JCI: Can you tell us a little bit about your path towards becoming a doctor? Friedman: I grew up in the suburbs of New York City with no great expectations for anything other than muddling my way through life. In my family, the expectation was that, if you were reasonably good at school, you'd end up being a doctor. After finishing high school, this was the path I found myself on and ended up completing medical school and doing a residency. At that point, I realized I wasn't so enamored of the idea of being a doctor. I found my way into science. In those days, you needed to apply for medical subspecialty training about a year in advance and I missed the deadline. When my medical residency was about to end, I didn't have any actual plans with what to do [...]

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*JCI*: Can you tell us a little bit about your path towards becoming a doctor?

Friedman: I grew up in the suburbs of New York City with no great expectations for anything other than muddling my way through life. In my family, the expectation was that, if you were reasonably good at school, you'd end up being a doctor. After finishing high school, this was the path I found myself on and ended up completing medical school and doing a residency. At that point, I realized I wasn't so enamored of the idea of being a doctor.

I found my way into science. In those days, you needed to apply for medical subspecialty training about a year in advance and I missed the deadline. When my medical residency was about to end, I didn't have any actual plans with what to do with a gap year. One of my professors thought I might like medical research and he referred me to Mary Jeanne Kreek at the Rockefeller University to try research for a year. She studied addiction, and I was really excited at the time about the idea that molecules could regulate behavior and emotion.

My project in that year was to develop a radioimmunoassay for  $\beta$ -endorphin. The only difficulty was that I had absolutely no idea how to even begin going about it. There was another investigator at Rockefeller at the time, Bruce Schneider, who was quite expert in this. I spent a good deal of that year working with Bruce, ostensibly to be developing a radioimmunoassay for  $\beta$ -endorphin. As it turns out, Bruce was interested in the role of cholecystokinin (CCK) to control metabolism and appetite. And, through that interaction, I learned a lot more about feeding behavior and the ability of CCK to reduce food intake in rodents. In fact, through Bruce I learned about the genetically obese (*ob*) mouse because some scientists – but not Bruce – believed that the obesity of this mouse was a result of a defect in CCK expression.

*JCI*: Did this time in the laboratory convince you to abandon medicine for research?

Friedman: During that year, I really fell in love with working in a laboratory. I was not sure what I wanted to do and I had a sense – this was 1980 – that molecular biology was going to have a big impact on the future of research and science. In order to figure out what to do, I wrote letters to a series of people who were well practiced in the black arts of molecular biology. The most useful reply I received was from David Baltimore, who didn't know me at the time and wrote back and said that he thought the Rockefeller PhD Program was very well suited to someone with my background. With that, and other inputs that I'd received, I decided my best course was not to return to medicine but rather start the PhD Program at Rockefeller, which I did in 1981. I joined Jim Darnell, who was also one of the early leaders in the burgeoning field of molecular biology.

*JCI*: How did you fixate on *ob* as your target?

Friedman: In Darnell's lab, I was studying liver gene expression. But I carried with me an interest in the *ob* mouse. And so, apart from my PhD studies which focused on liver, together with Bruce and another fellow, Don Powell, we cloned the CCK gene in 1983. The main reason we cloned it was so that we could position it on the chromosome map. And in 1983, with the newly-cloned CCK gene in hand, we worked with another scientist, Peter D'Eustachio at NYU, who was able to use a technique known as somatic cell hybrid mapping to position CCK on mouse chromosome 9. This was important because *ob* mapped to mouse chromosome 6 and so this excluded CCK from being the causal defect in the *ob* mouse – settling a controversy. This then raised the question about what the primary defect actually was, and when I started my own lab in 1986 it was with the idea to positionally clone the *ob* gene.

*JCI*: Can you tell us a little bit about how the events unfolded towards your actual discovery?

Friedman: We segregated the mutation in large genetic crosses it so that we could map DNA markers relative to the mutation. We were able to find markers that mapped within 0.1 cM of *ob*. And with that as a starting point, we cloned the DNA in the region of that marker, looked for genes and ultimately found one that was defective in the *ob* mice.

One of the genes in the region was completely fat-specific. We had spent a lot of time imagining where the defective gene might be expressed; no one really knew. One of my great concerns was that it might be expressed in a tiny cell type that would make it rather elusive. Nonetheless, when we saw a gene expressed exclusively in fat – that captured our attention.

*JCI*: What was the moment of discovery like?

Friedman: It was pretty freaking awesome and it was really one of the great moments of my life. As a series of exciting but preliminary experiments unfolded, I myself developed a blot at about four in the morning. The result was pretty striking and clearly indicated that we had in fact cloned *ob*. Our findings were also consistent with a prior hypothesis put forth by Doug Coleman of the Jackson labs, that the *ob* gene encoded a hormone that was under feedback control.

*JCI*: Doug Coleman stated that it took him years to overcome the dogma that obesity was not just a problem of willpower but that there was a molecular determinant. Together, the two of you managed to change people's minds. For that, you two were awarded the 2010 Lasker Prize.

Friedman: There was no professional moment I've ever had that matched that moment of developing the film and seeing the actual results. Other people have said it in their fields, and it was true in mine, I mean you're looking at blobs on a blot that are uninterpretable to most other people who were not used to looking at things in that way, but it revealed a really elegant and simple biological system configured by nature that, to me, is incredibly beautiful. I sometimes think that recognition of the sort like the Lasker is, in part, really nice because it reminds you of that moment.

*JCI*: Amgen licensed leptin from Rockefeller, but they terminated their clinical trials using leptin as a treatment for obesity. You've stated that you could have predicted that it wasn't going to be a panacea given that most people produce leptin. Do you think there's ever going to be a pharmacologic magic bullet to treat obesity?

Friedman: Yes, I think there will be treatments, but the story of leptin as a potential treatment for obesity and its potential as a future agent for other conditions is a little complicated. Leptin's job, in a sense,



**Figure 1**  
Ushma Neill interviews Jeffrey Friedman in New York City on December 10, 2012. Image credit: Semyon Maltsev.

is to maintain homeostatic control of fat mass and this has important evolutionary considerations because it allows organisms to maintain a relatively stable weight, balancing the relative risks of being too thin which is starvation, or being too fat which leads to susceptibility to predators.

In the *ob* mouse, and similarly affected humans, there's a mutation in the gene, so there's no signal that's ever generated that there are adequate fat stores, and animals and humans who have leptin mutations overeat voraciously. In both cases, if you replace the leptin, body weight normalizes. Leptin as a treatment for leptin deficiency is extremely robust, very potent, works beautifully, and it works very well for other leptin deficiency states beyond leptin mutations. However, most obese humans and most obese animals are obese for reasons that lead them not to be leptin-deficient, but rather lead them to be leptin-resistant.

We knew very early on that diet-induced obesity, which is thought to represent an animal form of human obesity, was associated with high leptin levels and leptin resistance. We were skeptical about what the clinical utility of leptin would be in a case where there are already high endogenous levels. It turned out that leptin, by itself, is not a particularly effective antiobesity agent in that setting. We now know that the people in that trial may have been getting too much leptin because a subsequent trial, with lower doses paradoxically, had a greater effect.

The most recent findings would seem to

suggest that if you pair leptin with another agent, in this case the peptide amylin, you can get very robust weight loss. It remains to be seen whether that combination emerges as part of the clinical armamentarium for doctors treating obesity. I'm pretty confident however that, as a deeper understanding of the neuronal circuits that respond to leptin is developed, new treatments will emerge.

*JCI:* In 2003, you wrote a perspective piece called "A War on Obesity, not on the Obese" for *Science* wherein you commented about the societal implications of weight gain. Are we currently in an obesity epidemic in the United States?

Friedman: What we really have is a highly prevalent medical condition that needs to be addressed to the best of our ability to do so. The reason that people refer to this as an exploding health problem is that if you simply count the number of people who exceed a threshold of BMI greater than 30, you can see a steady rise over the decades that seems pretty significant.

The problem is that it's well established in epidemiology that if you have a distributed trait and a fixed threshold above which you refer to an individual as having a disease, the curve doesn't have to move very far for you to get a huge increase in the number of people who exceed that threshold. So, over the same intervals where you see dramatic increases in the number of people over BMI 30, the curves actually haven't moved that far, which means that average weight hasn't changed very much. In fact, over the same

intervals where obesity rates are said to increase over a third, you see maybe a 7- to 10-pound weight change.

*JCI:* Do you think that there is a need for changes in behavior and pharmacological intervention?

Friedman: The question is what would you tell an obese person now had a health problem? It turns out the things I would tell an obese person now are pretty much the same things I would tell a lean person, or a person of average weight. Eat a heart-healthy diet, exercise, and if you are overweight and have a comorbidity, do your best to lose a modest amount of weight, say 7 to 10 pounds, because that's often enough to improve your health. I don't think there's any cause to tell someone who's greatly overweight that they need to have a BMI of 22.

Pharmacological therapy should be reserved for those cases wherein less extreme recommendations are not working. The point here is that most people operate within a range and 10- to 20-pound weight loss that is difficult but achievable. For those who are most severely afflicted by obesity and its comorbidities, weighing 50 or 75 pounds above ideal body weight, behavioral measures are generally inadequate and that's where pharmacologic interventions would probably be best considered.

*JCI:* What do you think are the most important ingredients in being a good mentor to young trainees?

Friedman: I don't know what the right answer to that is. I can tell you the way I like to run my lab, which is that I want people to really play as active a role as they can in developing their own ideas and their own programs. I like to think of each of the people in my lab as sort of a PI who doesn't have to raise their own money. And so, I think people do better, and are most invested, and learn most by feeling as much ownership as they can of what it is they do. I, to a large extent, view my role as enabling them to the extent I can to pursue the things they're most interested in.

*JCI:* What would you choose if you were to pursue an alternate career?

Friedman: When I was a boy I wanted to be a veterinarian, as I love dogs, but I could imagine myself studying history. I could also imagine myself as a sports writer. Being a professional athlete is probably out of the question because it requires some ability. I could be a bartender, but I think I'd probably consume too much on my own.

**Ushma S. Neill**