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AS TOLD TO
Dr. Kieran Murphy



Renowned doctors Kieran Murphy and Daniel Drucker discuss medical creativity, innovation trajectories, and systemic barriers in health care in this fascinating discussion.

DR. DANIEL DRUCKER'S literal gut instincts are changing the world. A physician-scientist based in Toronto, Drucker is one of the world's leading experts on gut hormones—tiny chemical messengers with a huge impact on how bodies manage blood sugar, absorb nutrients, and control appetite. His discoveries have transformed treatments for diabetes, obesity, and serious digestive disorders, touching the lives of millions around the globe.

For decades, scientists suspected that hormones made in the gut played a bigger role in overall health than anyone had realized. But it was Drucker who connected the dots and uncovered how certain gut hormones—especially glucagon-like peptides, or GLP-1 and GLP-2—could be harnessed as powerful medicines. Drucker and his team were the first to show that GLP-1 stimulates the pancreas to release insulin—but only when blood sugar levels are high. He also discovered the key actions of GLP-2, which helps the intestines grow and absorb nutrients. That breakthrough led to teduglutide, the first long-term treatment for people with short bowel syndrome. Drucker identified the enzyme DPP-4, which breaks down GLP-1 and GLP-2 in the body. His research showed that blocking DPP-4 could help these beneficial hormones stick around longer, which in turn led to the development of DPP-4 inhibitors.

With more than 33 U.S. patents, groundbreaking discoveries, and countless lives changed, Drucker's name is etched into the history of modern medicine. He holds prestigious roles as a professor of medicine at the University of Toronto and was previously the Canada Research Chair in Regulatory Peptides. He has received the Wolf Prize in Medicine and the Canada Gairdner International Award, and is a fellow of the Royal Society, a member of the U.S. National Academy of Sciences, and an Officer of the Order of Canada.

In a world hungry for medical breakthroughs, Drucker stands as a shining example of what happens when curiosity meets compassion, and science meets service. In an exclusive interview with Dr. Kieran Murphy on behalf of *Lifestyles Magazine/Meaningful Influence*, Drucker discusses his career path, the magnitude of his work, and the creativity of medicine.

KIERAN MURPHY: You're part of a small group of people in the world who have changed the practice of medicine. People don't see medicine as a creative art often when, in fact, it's a phenomenally creative field. How has medicine allowed you to express that creativity and discover the things that you found?

DANIEL DRUCKER: In my field or the science that we've done, I would not say that it replaced things that were done badly. In seeking to understand how things work, we stumbled across new hormones and new mechanisms that allow us to treat people better. In hindsight, one might say, "Well, they weren't treated as well before," but we did have options for some of the disorders I've worked on. But some of them have been shown to be just completely outdated and inadequate. Either GLP-1 medicines or GLP-2 medicines have changed lives and changed outcomes, and that simply stemmed from curiosity.

I'm an endocrinologist. We try to understand how endocrine disorders arise and how hormones work. That's the basis for the good fortune I've had in being able to do the science that we've done.



sequence of the gene. I felt extremely sad because I was supposed to do thyroid research. In fact, mythyroid.com is still my website, and I looked after people with thyroid disease for the better part of 25 years. But I was stuck working on the glucagon gene and pivoted toward a project more related to metabolism than thyroid.

As it turns out, that happened to be the biggest, luckiest break in my life that changed my career and changed my life.

KM: One of the things that is so formative in our careers is our fellowship and who we choose to do our fellowship with—sometimes that's a random decision. It may not be as exact as we think it is; I was given a topic to work on that I didn't want to do, but I became interested in it. That topic: vertebroplasty. How did you choose your fellowship and your mentor?

DD: I had a wonderful mentor in Toronto named Gerry Burrow. He was the physician in chief, chair of medicine, and arranged for me to interview at three different labs. I was supposed to do thyroid research—Burrow was a thyroid specialist. I interviewed at three labs that did thyroid research, including the lab where I ended up at Massachusetts General Hospital.

When I got there, the thyroid project was moving to another hospital in Boston. So I was left with a fellowship to work at Mass General, but no thyroid project. I was to work on the glucagon gene and figure out these new glucagon-like peptides that are predicted to be released, based on the

KM: Winston Churchill said people have moments where they discover something—some keep moving and others identify the significance. Did you have a moment like that where you realized you were doing something that was potentially significant, or were there moments of insight?

DD: I think it was both. In the 1980s, one of our first experiments showed that GLP-1 (glucagon-like peptide-1) stimulated insulin secretion, and did so only when the blood sugar was elevated. We identified the precise form of GLP-1 that did that. It was the first description of biological activity for this new hormone. It was apparent to all of us that something stimulating insulin secretion might be useful for the treatment of type 2 diabetes. It took 18 years to go from the basic science to the clinical science and ultimately drug approval, overcoming obstacles along the way.

And then, 10 years later, there were three groups, including my own, that discovered that GLP-1 also reduces food intake. Maybe that would be useful for the treatment of obesity. That also took 18 years to go from initial observation to first drug approval. Similarly, we discovered that GLP-2 stimulated the growth of the lining of the intestines. We thought that might be useful for the treatment of people with intestinal failure who need more gut to absorb their nutrients. That took about 15 years.



Drucker and his wife, Dr. Cheryl Rosen, at the Breakthrough Prize ceremony

So there were moments of insight and “aha” moments in the lab. But as we know, it’s not easy to make a drug, and it often takes a long time. The hurdles and obstacles to overcome are sometimes considerable. So we had moments of exhilaration and then months and years of despair and frustration, but ultimately the stories turned out well.

KM: One thing I’ve underestimated is how long it takes for an idea to go from a moment of insight to being adopted by all your colleagues to eventually reaching a point where it’s seen as logical. Physicians are very slow to adopt. It could be 10 to 20 years, easily.

DD: I agree. This is one of my major issues I focus on now, having realized that it’s not useful to discover something and help it become a drug if it’s not being used effectively to improve people’s health. We call this therapeutic inertia: Unless doctors and physicians learned about this early on in medical school, or they were directly involved in bringing this new type of intervention or medicine to market, they are slow to change their prescribing habits and change the way they practice medicine.

It’s fascinating to study this. Patients are often reluctant to take new medicines, even if they’re not expensive or have proven benefits. The area that I

work in—we treat people with type 2 diabetes, we treat people with obesity to reduce complications years down the road, and it can be difficult to convince people that the medicines they’re taking today will have a tremendous effect on them in 10 or 20 years from now. Beyond the prescribing gaps and the therapeutic inertia, we have challenges in persistence and adherence and convincing people to take these medicines. We have to make these innovations as effective as they can be for people and for society.

KM: In May, I watched the Indianapolis 500 and there was a racer who’s a type 1 diabetic. He spent three hours in a car with a monitoring system broadcasting to the steering wheel what his serum glucose was. His insulin pump delivered the appropriate amount of insulin and he had a water bottle with some sugar in it, keeping his levels at the right level. It’s a phenomenal achievement to see a high-performance athlete managing that disease in that context. Did you ever envision it being something that could be managed that well?

DD: When I started as a young endocrinologist, our ability to manage diabetes with technology consisted of being able to take some urine and check whether there was some glucose in the urine. Absent that, we had to actually poke a needle into someone’s



arm and send the blood test off to the lab. That was in the early 1980s, not that long ago. Then we had the first glucometer, a device that could non-invasively measure blood sugar levels with a drop of blood. But the size and weight of that glucometer—it was around 20 pounds and only the most sturdy, robust endocrine fellows could carry it around the wards for hours. The smaller among us couldn't manage it.

Today, we've come so far with non-invasive monitoring coupled to pumps that tell us how much insu-

lin we need, and have algorithms that will predict what our insulin needs would be. It doesn't mean that we've fixed type 1 diabetes, but we've made it more manageable to live with.

There's a race: stem cell biologists trying to generate these fantastic insulin-producing stem cells that would make this technology unnecessary, versus this amazing tech for sensing glucose and coupling it to insulin delivery that engineers are spearheading. Engineers have so far been winning that race. What we would love now is for biologists to catch up and continue to excel at what they're doing. But it's transformative positive change for people with type 1 diabetes over just several decades.

KM: I'm curious about if you could go back to that moment: You're in Boston, you're at Mass General, you're working on glucagon and looking at the visual products of glucagon. What was the discovery like?

DD: We were excited we found that GLP-1 stimulates insulin secretion. The magnitude of the potential importance was brought home to me when I came in a few weeks later and my notebooks were gone. I thought, "Oh, my God, someone's broken into the lab and stolen my notebooks. This is a disaster!" But then my supervisor, Joel Habener, told me, "Don't worry, we needed your notebooks because we're filing patents and the patent lawyers want to look them over." As a trainee, I probably said to myself, "What's a patent?"



I was also a young physician without a job, without a secure future. As you know, many of us go into training and we have no idea what's going to happen to us. As excited as I was about the GLP-1 discovery, I was more excited that maybe we could publish papers—maybe that would make me attractive to an institution that would want to give me a real job, a better-paying job.

So it was a mixture of practical insights that this might be helpful for my career, as well as excitement about the actual discovery itself.

KM: The genealogy of the work you did—it's rare for an idea to come out of nowhere. How did your GLP-1 work come about?

DD: I was fortunate because the GLP-1 story started with the cloning of the cDNAs and genes in the late 1970s and continued in the early 1980s. We didn't know that something like glucagon-like peptide-1 or glucagon-like peptide-2 ever existed. But when the genes were cloned with this new technology of molecular biology, we saw sequences that predicted the production of these new hormones. Without those genes being cloned, I would never have had a project.

I was lucky that the lab I worked in, ostensibly for thyroid but ultimately for glucagon, had just cloned the gene for glucagon. Lo and behold, there were two sequences that no one had ever seen in the DNA, and they predicted the production of GLP-1 and GLP-2. So I was in the right place at the right time with the right material, and that was thanks to my supervisor, Joel Habener, who had gone to MIT in the mid-1970s to learn molecular biology and brought it back to Mass General and then set about

to apply it to endocrinology. He identified genes important for the thyroid and pituitary, but also glucagon and other hormones such as vasopressin.

So much of it was being in the right place at the right time. Having predecessors who did some of the early work enabled us to take the story to the next level.

KM: How do we create an environment where moments like that are likely to happen more often?

DD: A huge number of the discoveries that ultimately transform our health and the health and welfare and success of society start with basic science and start with fundamental questions that most of us would say "has no immediate practical relevance." Whether it is the internet, or electronic vehicles, or understanding climate change, or some of the marvelous cancer therapy and CAR-T therapy, and so on and so forth—these didn't start with people saying, "I'm going to invent this." They started with basic curiosity-driven research, then had applications, whether it's artificial intelligence or

applications that one could not have conceived from the get-go. How do we create this environment? We support basic science discovery research, whether it's chemistry or medicine or physics or mathematics.

We put in place funding to allow people to chase crazy ideas, to really have imagination, and to allow them to let it run wild and to apply it in ways that many of us may not think is logical. That's how we get the serendipity and the amazing discoveries that then go on to transform society.

KM: Before I came to Canada, I was used to a structure where the dean and the CEO are often one. Then as a practitioner, you work for the institution. Your promotion determines your salary and your promotion is determined by metrics of collegiality, academic output, teaching, clinical work, etcetera. And if you don't meet those metrics, you get fired.

In Canada, we have jobs for life, which I fear creates an environment more supportive of people who are good enough but not great, and then when people have truly great talent and research, often we don't support them. Our private group structure doesn't give them the protection they deserve. What are your thoughts?

Drucker in his laboratory at the Lunenfeld-Tanenbaum research Institute, Sinai Health



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DD: I think you're recounting a lived experience, particularly in Toronto—the way the medical school is set up, which tends not to devote a large amount of resources to the clinical departments, yet would fund basic mathematics or chemistry or physics without hesitation. I think what you're also recounting in part is a bit of a Canadian mentality that research funding is, in a sense, to be distributed quite evenly geographically across the country, without a heavy dependence on merit and excellence, but just to make sure that every region has some funding. We see this in Canada—some of our funding agencies state you can only apply and hold one grant at a time, and you can't have two grants. So, if you get your first grant and then you have a brilliant idea that could change the face of your field—well, you're out of luck because everyone wants to be fair and fund as many people as possible. There's less of an emphasis on excellence and more on how everyone needs to be treated fairly, regardless of output, regardless of exceptionalism.

I think that's, in part, a Canadian approach. We tend to be a kinder, gentler, more equal, focused society. But those ingredients don't provide the success and recipe for excellence that other systems might—it doesn't reward excellence to the same extent as other environments. If you don't reward it, you don't stimulate it, you don't foster it, and you tend to maybe revert to the mean as opposed to having fewer but more excellent individuals.

KM: Is there any standard advice you give your mentees?

DD: I try to instill in them the importance of asking good questions, which sounds silly because I think every scientist would say that they ask good questions. But I try to elevate the importance of the question. Is it the most important thing you could be doing right now? Will the answer, irrespective of whether it's positive or negative, transform our understanding of the issue? Will there be hundreds if not thousands of people in your community interested in knowing what your answer is to the question? If you can say yes to all of those, it's probably a good problem you're tackling.

Another is to do rigorous, reproducible science. Again, most scientists would say, "Well, of course, we all do rigorous, reproducible science." But the answer, unfortunately, is that some people do it better than others. Not everything you read in published scientific literature is reproducible and tends to lead to wasted time. We're careful about asking good questions, and we're even more careful about taking the time to get it right. **LM**