



DANNY LENNON:

Here we are. Professor Le Roux, thank you so much for joining me on the podcast. It's an absolute pleasure and an honor. Thanks for doing this.

CAREL LE ROUX:

Thank you.

DANNY LENNON:

There's a lot that I want to ask about, and I think before we get into any of those specifics, anytime we discuss obesity, it's probably worth framing that and kind of setting the scene of it, and I know in a number of your publications and presentations of yours that I've seen, you've been very clear to impress upon people, not only is this a complex and chronic disease, but the neurological nature of it is something that maybe is sometimes overlooked. Can you just maybe set the scene on what we're dealing with here, when we think of the disease of obesity?

CAREL LE ROUX:

Really, our thinking has changed dramatically when we think about obesity. So the first point that you've made is that we think now of obesity as a disease, and this is a disease of the part of the brain that you and I cannot control by thinking. So it means that neither of us can think ourselves less hungry or think ourselves more satisfied. Now, that's a really important insight, because it means there's nothing I can

say to you, that is going to change this disease. So if I want to treat this disease, I need to use normal physiological mechanisms to change it. The World Health Organization now defines obesity as excess adipose tissue that causes a deterioration in health. So let's break that down. That means excess adipose tissue, that could be adipose tissue subcutaneous or it could be visceral or it could be ectopic. So it's any excess adipose tissue. But for it to be a disease, it needs to cause a deterioration in health, so it has to have a complication. So we are not talking about people who just have a lot of excess adipose tissue, we're talking about people who have excess adipose tissue that causes a deterioration in health. So that helps us to frame obesity, because to treat obesity, it's not about weight loss, to treat obesity, it's about health gain. So how do we reduce the excess adipose tissue to then cause an improvement in health?

Now, the reason why we're flicking between these ideas about obesity as a disease that causes a deterioration in health and now thinking about the causes of obesity, it's only when we treat obesity as a disease in the organ that is responsible for the disease that we are really effective. So what I mean with that is we need to treat obesity to reduce these symptoms and the symptoms is what we refer to is the excess in hunger or a reduction in satiety. So let's break it again down into the essence, all diseases have symptoms, all diseases have signs, and diseases have complication. The signs of obesity is easy, that's the excess adipose tissue. The complications of obesity, there's so many, there's more than 200, so that's things like type 2 diabetes or reduction in functionality or depression or sleep apnea, those are all complications. But when we think about the symptoms of the disease, now we are thinking about excess in hunger or reduction in satiety, and therefore, now we have the idea, in the context of obesity, what we have to do. So first of all, we want to reduce the symptoms, and that will allow us to reduce the signs,

which will reduce the number of complications we have. And just putting it in that framework helps us as healthcare professionals, because we are pretty good at treating complex and chronic diseases, but now we know what we have to do.

DANNY LENNON:

Yeah, I think that's fantastic. And I think that you'd a beautiful phrase in there of we're not trying to treat weight – or we're not trying to go for weight loss per se, but for health gain. And I think that's quite useful to maybe get rid of some of the debate or disagreement that sometimes crops up in this area. And so, when we're thinking about the goal of treating obesity as a disease, you've outlined a lovely framework for us to start discussing. But in terms of potential interventions that are out there, I think, oftentimes, at least in the general population, it's probably presumed that diet or activity are the only way to go about that, or, at least, it might even register that this is a disease to be treated per se. So how would you frame to people what the goal of treating this disease is, and I know you've already kind of touched on that, and then what potential avenues do we have to explore?

CAREL LE ROUX:

You're correct. And I think the first thing to say is we need to have sympathy with our patients, because this is a difficult disease, and we also have to have sympathy with ourselves as healthcare professionals, because this is not easy to treat. So having said all of that, there's also been some insights that's really revolutionized the way we think about obesity as a disease. So let's just take this assumption that we've had for many centuries, and the assumption was that overeating causes obesity; and now what we are actually realizing is that the opposite is true. And when I say opposite, I mean, the disease of obesity causes overeating. Now, if you view it from that perspective, then you will see that making people eat less does not treat the disease of obesity. But if you treat the disease of obesity effectively, the consequence of that or the read out of that is

that people will eat less food. So that helps us to frame our treatment, because what I want to do with my treatment is the first thing I want to reduce the symptoms, which is, I want to make people feel less hungry and more satisfied. Now, how do I know if my treatment has been successful? I know my treatment works, if the patient comes back and says, doctor, since you've started this treatment, it is so easy, I'm not hungry, I'm feeling more satisfied; AND you know what's happened, I eat less food; and you know what's happened, as a consequence of me eating less food, my body weight has reduced.

Now, viewing it from that perspective, makes treatment of obesity far more satisfactory for me as a healthcare professional and for the patient. Because the alternative view is that what I set out to do is to make people lose weight. And the way to do it is to make them eat less, and therefore all my treatments are focused on banging the patient over their head with a big stick, you shouldn't eat that, you should eat this, you should be more controlled, you should move more, and all of those is framed in a negative setting. And actually, it just ends up, it hasn't been successful. So for the last 2000 years, we've been asking people to eat less and move more, and for the last 2000 years, it hasn't worked. So it's time to reevaluate it and say, let's do something different, let's treat this disease, and then let's see what the consequences are. And what has revolutionized again our thinking in this way is when we use bariatric surgery to treat people with obesity, because the surgeons do an operation on the stomach or the small bowel, and as a consequence of the operation, the patients say to us within days, it's amazing, where did the surgeon operate, did they operate on my tummy or did they operate in my head, because all the effects of the surgery is actually in my head, I'm not hungry, when I eat, I feel full. And the one thing we never ever ask patients to do after bariatric surgery is to eat less, they eat less because of the

consequences of the operation. In fact, we spend time with them in asking them to eat more protein or to take in specific types of food, because we don't want them to lose weight too quickly. And another thing we never ask people after bariatric surgery in the first year to lose weight, they do that naturally.

Now, that's happened in surgery. But what has now happened with effective medications that's becoming available for the treatment of obesity, we hear exactly the same narratives from patients. So if a patient responds to a treatment like Mysimba, or a patient responds to a treatment like Liraglutide or Semaglutide, the patients come back and say, this is just so easy, I'm not trying, I'm not more motivated, I'm not more intelligent, I'm just less hungry and more satisfied. And now suddenly, I'm just normal, and I can just do things I always wanted to do, only eat when I'm hungry and stop when I'm full. So I think that is going to change the way we approach our patients, because it's going to change the way we approach obesity as a disease.

DANNY LENNON:

Yeah, I think that's a really useful way to frame it, because I think a number of our listeners will be familiar with, previously on the show, we've discussed some of the nutrition or lifestyle interventions, and as you have pointed out, the relatively poor success rate not only of weight loss in the first place, but particularly with weight loss maintenance in the long term. And yeah, there may be some things where we could increase the probability of success with that, and that make it better or worse, and then some individuals will do better. But still, it's relatively unsuccessful when you look at the current data, and it makes total sense, because, as you've outlined, there's still a degree of restriction that's needed at some time point, which is what people will push back against. One of the really interesting things that I've noted from your work is rather than try and look for, what is the intervention that is going to solve all these problems, instead taking, well,

how do we have a broader view of all these various different tools, and then either be able to use them in an overlapping fashion, or, at least, be able to selectively use them for the right patient at the right time. Can you maybe just talk to that a bit more?

CAREL LE ROUX:

You're absolutely spot on, because our diagnostic, when it comes to diagnosing the causes of obesity is very poor. So let's go back 50 years, half a century, and imagine we lived at the time when we thought that cancer was one disease, and 50 years ago, we were looking for the cure for cancer. But what has changed is today, we know that even when we think about breast cancer, it turns out that is at least nine different diseases that just happened to be inside the breast. And the treatment for breast cancer that is HER2/neu positive is completely different. It is a treatment for breast cancer, that's triple-negative, for example. And now we are just about taking the step to think of obesity as a disease, but the way I'm thinking of obesity, as obesity, there's lots of sub diseases, that just causes people to have excess adipose tissue.

So there's lots of different diseases that happens to end up with people having excess weight. So that means it is very unlikely that we're going to find one silver bullet, and what we really need is more treatments. We need more nutritional therapies, we need more exercise therapies, we need more medications, we need more surgical treatments. Because until we have a diagnostic test, a blood test or a genetic test that will tell me that person A is going to respond to treatment X, and person B is going to respond to treatment Y, until that day, we need all the treatments on the table. And if a patient, for example, doesn't respond to treatment X, then we can change the treatment Y. And so, we try to present all of the treatments, be it nutritional therapies, exercise, medications or surgery, we try to present this in equipoise to our patients. We say that all of these are valid treatments, and they have

advantages and disadvantages. And what we need to do is I would like you as the patient to be prepared to take all of these treatments, but I'm also prepared to say to you as the patient, you tell me where you want to start. So if you're a patient that says, actually, you know what, I've tried all the diets known to man, and I would like to go directly to surgery, like, let's do that. Because whether or not the patient makes that decision or I make that decision, we have a similar chance of being correct. Or if a patient says, look, I never ever want surgery, but I only would like a diet approach. We say, that's a really good idea, let's start without nutritional therapies. But if it does not work, keep an open mind, and we can always escalate at that time, to a medication approach or even a surgical approach. So a big problem with obesity is that people – there's a lot of self-stigma, so patients blame themselves for this disease, and therefore, when they are not successful with the treatment, they think they have failed. And they don't want to come back to the healthcare professionals because they think we, as healthcare professionals, will be angry with them and give out to them; and, in fact, what we have to say is, if it's not working, come back, because then we try something else, because now we are developing a range of tools in our toolbox, and we have to be prepared to use all of them.

DANNY LENNON:

If we maybe touch on surgery here for a moment, specifically, I think this is a really good example, especially for, again, someone in the average population who maybe isn't sure what is going on with surgery, or why it's working, there may be an initial misconception that it is, again, treating one of those signs of obesity that you mentioned, in that, surgery is there's there to reduce the amount of adipose tissue because doing something at physical like restricting how much someone can eat. But rather we know that there's actually a lot of really interesting physiological responses that happen post-surgery, and again, that could be a whole long discussion in itself, but just from an

overview level, how would you tend to introduce what we know happens post-surgery in some of these surgical interventions?

CAREL LE ROUX:

The best way to explain this is to relate it to the patient's experience. So very often, we will ask patients when you start eating, how long does it take you to stop; and patients will very often say, that's my real problem, when I start eating, I have to consume a large number of calories before I feel satisfied. And what we are then able to explain to the patient is that's exactly one of the major problems with obesity, because the way the gut talks to the brain as being interrupted or it's just suboptimal. When you eat food, the signal that goes from the intestine to the brain, to tell you you're feeling satisfied or full is not good enough. And what surgery does is it enhances this natural signal. So when we have an operation such as a gastric bypass or a sleeve gastrectomy or even gastric banding for that matter, what we find is that patients report that they feel more satisfied with fewer calories, because we've enhanced the way the gut talks to the brain.

Now, patients intuitively understand it, because they live with this problem of not feeling satisfied after meals, and they don't understand why it is that other people could eat higher fat food and high sugary foods, but they consume lower volumes of it, because they just feel satisfied. But if we can change that signaling system in the gut by using a surgical treatment, that is really powerful. Now, the benefits of surgery is it doesn't only work through hormones, it also works through the nerves and the neural signals to the brain. It also works by changing the gut microbiota. It also works by changing the bile acids. So what makes surgery so effective is that it has multiple mechanisms, and therefore, the majority of patients go on to lose 20, 25 or 30% of their body weight, because we have more than one mechanism in play, where, if we, for example, use a medication or use even a nutritional therapy, we will have a smaller

number of people that can get 20-25% weight loss because that therapy is very successful for that patient. I think that's an important point also to stress at this point in time is that we say to our patients, if we give them a nutritional therapy, and they go on to lose 20% of their bodyweight, it is not because they are morally superior. Equally, if we give them a nutritional therapy and they lose no weight, it's not because they're morally inferior. It is biology. And the patients normally laugh when you talk about the moral superiority, but when you then switch and talk about the moral inferiority, it's sort of like a penny drops, because they have been told they are morally inferior, they are not good citizens, because they're not controlling themselves. And by shifting that and taking that blame away, gives the patient's agency.

So we've actually set up a website called itsnotyourfault.ie, and the reason we've done that is to communicate to patients that this is a disease, that's not their fault, but it is their responsibility, and it is my responsibility to find a treatment that works. But if the treatment doesn't work, that's not their fault either. It just means that we have to go back, and again have the responsibility to find a treatment that works. That makes again this process of treating a chronic disease far more effective, but also far more pleasurable for us as healthcare professionals, but also for our patients.

DANNY LENNON:

Fantastic. So with surgery, we have multiple mechanisms of action that are leading to some of these results, whereas with medications, as you've just touched on, would seem to be a bit more targeted in their specific mechanism of action. Across the various drugs that are currently available, do they all work via similar means, do we have differences among them, is there scope for future drugs to target different mechanisms – what's the kind of current state of medications in this area?

CAREL LE ROUX:

Yeah. So we have very few medications for obesity that is approved, and the medications we do have work on very different mechanisms. So, for example, we have medications such as Orlistat that's a lipase inhibitor, and we have medications such as Mysimba which is a combination of naltrexone and bupropion, those are centrally acting drugs, small molecules that work on centers of the brain that predominantly reduces hunger and reduces cravings. And then we have the GLP-1 analogue class Liraglutide and Semaglutide which predominantly works also in the subcortical areas of the brain, but appears to be driving fullness or satiety, while also reducing hunger. So what you can see is these different mechanisms, but the classes of medication that appears to be most successful, all go through this common pathway, most likely situated in the hypothalamus, by changing the neuronal signals in the NPY neurons and the POMC neurons, ultimately resulting in changes in symptoms of the patients, making people feel less hungry and more satisfied. So yes, there may be different mechanisms to achieve that, and we need more drugs that will address different mechanisms, but ultimately it is going to be successful if it goes through this common pathway in the hypothalamus by making people feel less angry and more satisfied.

DANNY LENNON:

Fantastic. On a pragmatic level for people who are working with patients, given what you've said about these range of different interventions that may now be possible, and ideally getting to a place where we're choosing the correct treatment for the right patient at the right time, pragmatically, what might that look like? In other words, for those who are working with people, is there anything that, apart from trial and error, do we have anything systematic at the moment to go through that process of working out what's correct for someone? Or for maybe dieticians listening, is there a role for integrating dieticians alongside someone's GP, alongside their obesity medicine specialist? How might this work in an ideal

world, which I know is very different to maybe what we're currently in – what could you envision that looking like?

CAREL LE ROUX:

So I think the first thing we need to do is to just put obesity in the same box as any other chronic disease. So imagine we take another chronic disease such as type 2 diabetes, what we would do for type 2 diabetes is we would have wide ranging public health interventions. So people could do that themselves, so this is better diets, better exercise, to prevent the disease, etc. But if that does not work, so people have tried the public health interventions, that doesn't work, we escalate and very often we have professionally directed changes. So that could be a nutritional therapy or an exercise therapy for type 2 diabetes. Now, if that doesn't work, we can escalate to adding medication. And we have different classes of medication in people with type 2 diabetes. Sometimes just starting on one class, it's more than sufficient to control the patient; but if that is not sufficient, we can add a second class or we can stop the medication and add another class of medication. And if that doesn't work, we can escalate to a surgical treatment, and we know that surgical treatments can place diabetes into remission in the long term, in a large number of patients. And, of course, even if that doesn't work, if somebody has surgery or diabetes, but the diabetes relapses we can add medication on top of the surgery. So we actually have paradigms that work very well for chronic diseases. I use diabetes as an example, but we can use exactly the same for hypertension, that's another chronic disease, or dyslipidemia is another chronic disease.

So if we actually think about what we need to do for obesity is we just need to do exactly the same. Right? So we need more public health directed messages where we can have public health interventions that can prevent people developing the disease. But once they have the disease, they need to be escalated to the next level, and that could be professionally directed

lifestyle changes, that could be nutritional therapy, exercise therapy. Now, we know within three months whether or not this treatment is going to work or not; and if it works, we continue; and if it doesn't work, then we escalate to the next level, and that could be adding a medication. It turns out with medication, we know within three months if it's going to work or not. So if you start with medication X, and it's not working, then stop it after three months and go to medication Y. And if that's not working, stop it and go to medication X or Z rather, if I can remember my alphabet. And if the medications don't work, escalate to surgery.

So what we want to do is we want to use the same processes that we work through, but what we want to change is how long we force people to remain in that zone. So let's not force somebody to remain in the professionally directed nutrition and exercise approach, if it's not working, escalate them to the next level. If we give them medications, and it's not working, don't keep them going around and around in circles **without** benefit, escalate them to the next level. So we want to get to the treatment that works faster, but we can follow our normal processes.

DANNY LENNON:

Yeah, that's really useful. And again, I think it's changing how people may view obesity, say, relative to some of those other chronic diseases, because as you mentioned, we wouldn't get someone to feel like a failure, if they had their LDL cholesterol through the roof, and it wasn't coming down via dietary changes, we would quite easily give them a statin and people would be happy to go on a statin. Whereas there seems to be much more resistance in this area, and given that we have a disease that people have real consequences of, and we have efficacious treatments that are probably very underutilized, one would imagine, it's quite a strange such situation, but one that is hopefully changing. Professor Le Roux, we are just coming up on time here, so

for people that are maybe interested in finding more of your work or looking at some of your publications, is there anywhere on the internet you'd like to direct their attention before we finish?

CAREL LE ROUX:

Well, thank you. So we set up the website called itsnotyourfault.ie to highlight some of the latest science, and we have the same handles on Twitter and Instagram as well as Facebook to try to promote this idea that obesity is a complex and chronic disease but that we now have the tools to treat it, and that we are able to move to this personalized medicine approach where we can get the right treatment to the right patient at the right time. And this is a hopeful space to be in, and I think a really interesting place for healthcare professionals to put their efforts into, because it's very rewarding to treat such a complex disease, and it's also very helpful to our patients. So thank you again for this opportunity to share some of the ideas and thoughts with you.

DANNY LENNON:

Yeah-no, it's been fantastic, and I very much appreciate everything you've put across today and your ongoing work is obviously very important. So thank you for doing that and for being part of the conversation.

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