

Episode 40:
Symptom Management Update
Transcript

If you're new to NETWise, we highly recommend you go back and listen to the first episode in this series. It goes over the basics of neuroendocrine tumors and how they're treated. And you can find a whole library of episodes on different topics at netrf.org/podcast, where you'll also find infographics and videos that expand on this material.

If you have a story to tell about your own NET journey, please email us and let us know - podcast@netrf.org.

You're listening to NETWise. I'm Jessica Thomas, Director of Patient Education at NETRF.

In each episode of this podcast, we share expert information and patient perspectives to help neuroendocrine cancer patients and caregivers navigate their journeys.

In today's episode, we're going to talk about some of the symptoms caused by functional NENs, and how those symptoms can be managed.

This is an updated version of an episode that we first published in 2020.

Welcome.

Neuroendocrine neoplasms can vary a lot from one to the next. Sometimes people can have NENs in their body for a long time and have no symptoms at all. Other times, symptoms caused by NENs can be uncomfortable, or even debilitating.

Often, these symptoms are the result of the unusual amounts of hormones some NENs can pump into the body.

Hormones are chemical molecules made by certain glands and

Episode 40:
Symptom Management Update
Transcript

cells. They circulate in the bloodstream and activate different processes throughout the body.

Here's Dr. Joseph Dillon, an endocrinologist and Medical Director of the Neuroendocrine Tumor Clinic at the University of Iowa:

***Dillon:** You can think of hormones such as adrenaline, testosterone, estrogen, cortisol, insulin which regulates your blood sugar, thyroid hormone which regulates your metabolism. The definition of a hormone is that it's produced in one site, in the body, gets into the bloodstream, and has a specific action at another site in the body.*

Neuroendocrine cells can produce hormones. And when these cells start growing out of control and become a neuroendocrine neoplasm, the amount of hormones they produce can become highly irregular.

Not all NENs secrete hormones, but the ones that do are called "functional NENs."

The waves of unnecessary hormones secreted by these functional NENs can have all kinds of effects on the body. Here's Caroline Creamer, a Physician's Assistant at the University of Pennsylvania:

***Creamer:** Our body's really good at maintaining a certain balance with our hormones and everything that goes on, and these tumors kind of take on a life of their own and start behaving outside of those normal regulatory systems, and then that's why when these tumors start secreting these hormones your body isn't able to contain it, because it's outside of that normal cycle.*

Functional NENs can secrete a number of different kinds of hormones, producing a variety of symptoms. A functional NEN can also produce multiple hormones at once, causing a combination of symptoms.

These tumors are often identified by the name of the hormone

Episode 40:
Symptom Management Update
Transcript

they most strongly produce. For example, a functional pancreatic NET could be called a somatostatinoma, because it produces the hormone somatostatin.

Dr. David Metz is a gastroenterologist who retired in 2021 from the University of Pennsylvania:

Metz: *Gastrinomas make gastrin that gives you excess of acid production and ulcer disease. Glucagon, which is the reverse of insulin, makes you get a high glucose level. Insulinomas make you get a low glucose level. PTHRP producing tumors, release a parathyroid hormone-like product that raises your calcium in the blood.*

Here's Dr. Michelle Kim, chair of gastroenterology at the Cleveland Clinic:

Kim: *And so, all of these different syndromes are different possibilities depending on where your primary tumor is located and depending on the hormone that is being oversecreted, so the symptomatology will really depend on what hormone it is that you're talking about.*

Probably the most common and well-known of these hormonal conditions is something called carcinoid syndrome. This is caused by an excess of the hormone serotonin.

Here's Dr. Aman Chauhan, an oncologist at the University of Miami:

Chauhan: *So our brain cells make serotonin. It is one of the neuro-transmitters, a fancy word for communication tools between two neurons. Outside brain or outside central nervous system (sic), It is produced in our lungs, in our liver, and our GI tract - very minimal quantities, just for normal functioning and normal growth of the tissue. Neuroendocrine tumors also produce serotonin. They produce it in a much larger quantity, and that's where the problem starts.*

Carcinoid syndrome mostly occurs with small-bowel NETs that have metastasized to the liver. This is because the liver is the

body's front-line defender against serotonin imbalance. Without the burden of metastases, the liver is able to break down the excess serotonin and control these effects.

Here's Dr. Eric Nakakura, a surgeon at the University of California, San Francisco:

Nakakura: *You typically don't get carcinoid syndrome until you actually have liver spread, because if you don't have liver involvement, usually the liver will break down the hormones and you won't have the carcinoid syndrome.*

Carcinoid syndrome can also arise from lung primaries, as well as some primaries and metastasis in the reproductive organs.

Nakakura: *When blood leaves the ovary, it bypasses the liver. It goes straight past the liver and into the general circulation. And so, if there's ovarian spread by an ileum neuroendocrine tumor, the hormones will bypass the liver, which would normally break down the hormone. And that's why in women who have the carcinoid syndrome, you not only have to look at the liver for possible involvement, but you have to look at the ovaries.*

One of the hallmark signs of carcinoid syndrome is flushing, a sensation of heat in the face and chest sometimes accompanied by a rash.

Chauhan: *Flushing is basically turning of skin color to either light pink, red, or dark purple. Typically it's a transient thing. It doesn't last long. In general, most of our patients don't really complain about sweating or diaphoresis with the flushing, they just turn red. A lot of time when I'm seeing patients in clinic, they would flush in clinic, they would not even realize until we point out to them or their family point out to them, 'see - you're turning red.'*

This flushing is sometimes confused with menopausal flushing, which can make getting a NEN diagnosis complicated for older women. But to a trained eye, these kinds of flushing are distinct.

Episode 40:
Symptom Management Update
Transcript

Kim: *Certainly not 100% type of thing that you can use to distinguish them, but generally speaking, the carcinoid flush does tend to be a dryer flush. The menopausal ones tend to be a wetter, sweatier flush. Again, we see some overlap there. So that's not 100%.*

Chauhan: *Carcinoid syndrome flushing is typically seen in head and neck region, face region, as compared to flushing seen, for example, in post-menopausal females, the flushing could be seen in the entire body.*

A more challenging symptom of excess serotonin is persistent diarrhea.

Creamer: *Really, oftentimes very terrible diarrhea. So they can go, they have to have a bowel movement, you know, 10, 12 times a day - which is really... really takes a toll on your quality of life. It can cause severe dehydration and electrolyte disturbances, weight loss, and malnutrition - probably more so because patients are terrified to eat because they think it's contributing to their diarrhea.*

Diarrhea can also be caused by a physical blockage in the intestine.

Nakakura: *Although the tumor or tumors are very small, they frequently spread to the lymph nodes in the region and form a mass called a mesenteric mass. And this mesenteric mass causes like a twisting and contorting of the intestine. People think diarrhea is from the carcinoid syndrome from the hormones like serotonin and other peptides or hormones that are released by these tumors, but when you have a high grade obstruction, this can manifest as diarrhea because only the liquid makes it through the intestine where the solid is backed up. So it's called post obstructive diarrhea, which is actually a symptom from a chronic or high grade obstruction. And oftentimes people will assume it's a carcinoid syndrome when in fact it's related to blockage. Or it could be a combination of the two.*

Flushing and diarrhea are the most common symptoms of carcinoid

syndrome. But other symptoms are possible as well:

Creamer: *They can also have other symptoms of, kind of, wheezing. It can cause something called 'bronchoconstriction', so the airways tighten up a little bit and can cause wheezing, as well.*

In about half of patients with carcinoid syndrome, a heart issue can arise. This is known as carcinoid heart disease. Dr. Eric Liu is a surgeon at the Rocky Mountain Cancer Center in Denver:

Liu: *So your tumor produces a lot of serotonin, if it comes from the liver, one of the first places it attacks is your heart - obviously a ton of blood flows through the heart - and the first valve that is inside your heart is called the tricuspid valve, and what it does is it kind of burns out the valve and scars it down so it no longer allows blood to flow in the right direction.*

When this happens, blood can begin to flow in the complete opposite direction.

Liu: *And let me tell you, that is not good for anyone's health. But that's an odd complication that not everyone recognizes, and so a neuroendocrine specialist can sometimes see that, treat it early - which requires heart surgery usually - get that fixed, and then the person can do better overall for a longer period of time.*

In addition to these physical effects on the heart and airways, excess serotonin appears to have a psychological dimension. There is a lack of significant research on this topic, but patients report a variety of symptoms.

Liu: *And so, when you ask a patient who has really very clear carcinoid syndrome, you know, related with the flushing and the diarrhea, they will tell you very consistently, 'I feel like I'm always in a little bit of a brain fog. I don't think as clearly. I have a hard time recalling words. My memory is not as good. Sometimes I'll get angry and fly into a rage without a good reason why. I don't know why.'*

Episode 40:
Symptom Management Update
Transcript

There are also mental health implications to dealing with the symptoms of this disease. Constant diarrhea can keep someone up at night, causing chronic fatigue. There might be some amount of pain. Flushing can cause embarrassment. Having a reduced ability to work, be social, or travel can also have negative effects.

Nakakura: *A critical point is quality of life, right? And the impact on not only the patient's quality of life, but their interactions with other folks, you know, their friends, family, and, you know, their work life. It can be very profound and then how they modify their life to deal with the symptoms they have.*

Fortunately, there are several treatment options available for carcinoid syndrome, and more are in the works.

The first-line treatment for most NENs is surgery. If the tumors can be removed completely, then the associated symptoms will largely go away.

Nakakura: *Even in patients with advanced disease and in an appropriately selected patient, surgery can also be very effective in not only controlling the disease and volume, but also the symptoms from the hormone excess.*

Tumor bulk can also be reduced surgically.

Nakakura: *This is one of the most remarkable and rewarding things that we do, is that if someone has a functional tumor, in particular carcinoid syndrome, and you adequately remove all the disease or debulk most of the disease, so very little residual tumor volume is left behind, those patients can go from having horrible symptoms to having zero symptoms.*

You know, I just saw a patient that I operated on several months ago who was having debilitating diarrhea, couldn't go on long car trips, couldn't travel, couldn't leave the house or go very far because that person had to be close to a toilet because of the diarrhea. Never knew when it was going to happen, you know, had issues with incontinence.

Episode 40:
Symptom Management Update
Transcript

You know, we operated on this person, removed extensive amounts of disease, leaving him with very low residual tumor volume. And that patient has no symptoms, none of the flushing in the face, which was, um, you know, he was very self conscious about it. And also the diarrhea, obviously. So it could be very profound where they, you know, the next day after surgery or that, you know, the recovery period from surgery, the diarrhea is gone.

There are also a few medications commonly used to treat carcinoid syndrome. The first kind of drug doctors reach for is a somatostatin analog, like octreotide or lanreotide. These decrease hormone production, which reduces the symptoms caused by the excess of serotonin.

Here's Dr. Ed Wolin, an oncologist at Mt. Sinai in New York:

Wolin: *Octreotide has been around for a pretty long time. It's a very important drug, approved in the United States for controlling both flushing and diarrhea from carcinoid syndrome, and it dramatically improves these things. The amount of flushing goes way down, the amount of diarrhea goes way down, and the production of 5-HIAA, which reflects serotonin production by the tumor, is reduced by about 50%.*

Another drug used to manage carcinoid syndrome is called Telotristat. This functions differently than somatostatin analogs.

Wolin: *Telotristat, which goes by a brand name Xermelo - this is a drug which blocks the production of serotonin. There's an enzyme we call tryptophane hydroxylase, that turns the amino acid we eat in our diet, tryptophane, it turns it into the precursor of serotonin that makes serotonin. If you block this enzyme, you stop production of serotonin and you can drop your production of serotonin by neuroendocrine cells by 50% over what is possible with somatostatin analogs.*

Creamer: *So the idea is that carcinoid tumors release serotonin and somatostatin analogs control that by blocking*

Episode 40:
Symptom Management Update
Transcript

the receptors on the tumor surface, whereas Xermelo works from the inside of the tumor and blocks the production of serotonin.

So, we want to make sure that their tumor is under control before we put them on that, because if their tumors growing and that's causing the symptoms, we want to address that first. But if they're stable and they're still having symptoms then this is something that we can add on to therapy and patients have done very well with it.

There is also research being done to create more drugs to treat carcinoid syndrome. For example, [there's an oral medication developed by Crinetics Pharmaceuticals that is currently moving into a phase 3 clinical trial.](#)

Other strategies may also help to alleviate symptoms related to carcinoid syndrome.

Dillon: *Those include attempts to cut off the blood supply to tumors if they are in the liver - that's the process called hepatic artery embolization. And indeed, PRRT - which is essentially radioactive Octreotide - that has also been shown to decrease the carcinoid syndrome symptoms along with decreasing the tumor bulk.*

Along with these treatment options, there are other things, like nutritional supplements, that can play a role in symptom management.

Wolin: *There's a drug.. I don't know if you want to call it a drug, you might call it a nutritional supplement, called Enterade. It's the mixture of five amino acids - valine, aspartic acid, serine, threonine, and tyrosine. These are just all the normal amino acids, the building blocks of your proteins, mixed with some, you know, generally accepted, tolerated sweeteners. It's made specifically so that all the nutrients are absorbed by the small bowel. There are people who have trouble maintaining nutrition because they have diarrhea all day and they can't absorb the food they're eating. But every amino acid that you eat in this mixture gets absorbed in the small intestine. You*

don't poop it out.

While there are a lot of treatment options for carcinoid syndrome, it can take patients a long time to receive them. This is because it often takes a while to get an accurate diagnosis for these hormonal symptoms.

Here's Dr. Heloisa Soares, an oncologist at the Huntsman Cancer Institute at the University of Utah:

Soares: *One of the frustrations of patients with carcinoid syndrome, in particular, is that some of these symptoms are not very specific and it can take some time for the physicians even to think about this diagnosis. As again, because they, many of them are so rare that it might not be in the top of the list of differential diagnoses of the physician.*

Liu: *The other challenge, too, is frequently the patient doesn't even realize what's going on. It's like, 'oh, well I have some diarrhea.' You know, 'I have probably some gluten sensitivity', or something like this. 'There's just stress in my life'. If you have a very slow indolent disease, which has maybe been growing inside you for 20 or 30 years, what it does is it slowly affects your life, so you don't almost notice it as it changes things. It may make your stomach hurt a little bit, it may adjust way you go to the bathroom, and it may adjust the way you think, and people will think, 'Oh, I'm just getting older.' People will think, 'Oh, I'm just not getting enough sleep.' 'Oh, I'm just not getting enough exercise', all these things. And so their life just slowly starts to change in a gradual, gradual way, so they don't notice.*

And it's not until you start to get them treated - you get them diagnosed, you get them treated with either hormone treatments, or surgical, or whatever it is, whatever they need to get their disease under control - they don't even realize how much their life has changed.

Fortunately, awareness about neuroendocrine cancer is increasing. More and more doctors are learning how to identify

the disease, which is reducing how long it takes to get an accurate diagnosis.

Soares: *So hopefully we are shifting the timing of diagnosis that used to be, you know... we have literature that says it can take up to, like, eight years for a patient to finally be diagnosed with a 'carcinoid', quote unquote, that hopefully now with better imaging and awareness, we're going to be able to treat these patients much earlier in the course of the disease, and then there is much less frustration.*

Patient Story #1:

My name is Maureen Edwards. I am from Hudson County, New Jersey, right near New York city. I'm 49 years old and I was diagnosed eight years ago with carcinoid syndrome.

I was symptomatic on and off, in retrospect, for two years - flushing, gastro issues, diarrhea. If I became anxious or stressed, my cheeks would be like, honestly, purple and it would feel almost like tingling and almost like needles in my cheeks. The day after Christmas break, I woke up and I couldn't get out of bed - tingles, neuropathy in my fingers and toes - which then began the journey of a bunch of doctors, which lasted a good year of going to what started with my primary, who did a battery of tests, and a week later the test came back... a test for serotonin. That was the first I ever heard of serotonin. So, the range for serotonin for the blood work, normal, was up to 200 and mine was almost 400. So, I then was referred to an oncologist in Manhattan. She heard my story, and basically started me on a protocol of Sandostatin. And when I had the gallium scan, I lit up strongly at the tail of my pancreas and in my liver, and I was referred to a surgeon who basically took out the sections... you know, as per the scan. So, I was on Sandostatin, which worked and I felt good for a while after the surgery. And then I... it stopped working for me for a while. So, I was on one shot every four weeks, then it was one shot every three weeks, and then that was not doing it. I needed a lot of rescue shots. So, we shifted after a while from Sandostatin - four years ago

Episode 40:
Symptom Management Update
Transcript

this is now - to Lanreotide, and I felt much, much better. After one or two shots every three weeks, I felt very, very good.

And then three years ago, my doctor had said, you know, since my serotonin was still up and I was still symptomatic at the end of my Lanreotide shot, she was saying that the, new medicine Xermelo would help me a great deal because that would help with lowering serotonin. And my doctor said it would be a game changer, and it WAS a game changer for me. So with the Lanreotide and the Xermelo, three years ago I was finally feeling human again. I could go out. I was not bloated. I was not in the bathroom all the time. I was not rushing all the time. So, the stresses of life were not so hard on me and I could function.

The symptoms of carcinoid syndrome can be brought on by stress, either emotional or physical. This can sometimes cause a massive rush of serotonin-related symptoms that can be triggered by some medical procedures, like surgery or even dental work. This is called carcinoid crisis.

Liu: *And the reason that happens is because... it's not the actual surgery itself. It's not the cutting, or the technique, or the sewing, that kind of stuff. It's actually the anesthesia. So, the medicines that we give for anesthesia, at the time of what's called 'induction', which is where they first go to sleep is a very stressful time for anybody. It would be the time that people, say, who are at risk for heart disease might get a heart attack or they might get a stroke or something like that. Of course, you know, we're very careful to check for those things. And what it can do is it can cause weird, weird things.*

It can cause what we call hemodynamic instability, which is basically problems with your heart rate, problems with your blood pressure, kind of just the general flow of blood through your body. And so, some people can... their blood pressure can shoot way, way up. Some people, their blood pressure can bottom out. Some people, their heart rate can drop. Some people, their heart rate can increase.

Episode 40:
Symptom Management Update
Transcript

Nakakura: *In some situations, it could be very, very critical where patients can have very dangerous high or low blood pressures.*

Traditionally, the treatment for this has been an octreotide infusion, and most doctors throughout the world, I would say, feel very comfortable having octreotide handy or given prophylactically, you know, before surgery or procedures to try to mitigate or prevent carcinoid crisis. However, there's been recent data coming out and has shown that even if you give the octreotide fusions, carcinoid crisis or wide swings of blood pressures can occur.

So anesthesiologists and the treatment team have to be aware that they can't just rely on octreotide as a magical panacea to prevent carcinoid crisis. Rather, they have to diligently follow the blood pressure and vital signs and give medications to normalize them.

Patient Story #2: *I'm Cy Ball. I live in Denver. I'm 72 years old. I was first diagnosed in, well, 2011 with what... at the time they diagnosed me as a mid-gut NET, which turned out to be false. They never found a NET in my mid gut, and then finally two years ago found one on my pancreas, which they figure now is the primary.*

Well, the reason it was found originally was because there was a tennis-ball-sized lesion on my liver that was discovered by accident in a CAT scan of my lungs because I had a cough, which turned out to be nothing, but the lesion on my liver turned out to be a NET.

I had symptoms that were not properly diagnosed of a burning stomach, light diarrhea, night sweats, stuff like that. I was told for five years, six years, (that) I took too much ibuprofen, is why my burnt... stomach burned all the time, or that maybe it was GERD or something, but they never actually did a real diagnosis. And I actually had a bleeding ulcer before the diagnosis. And it turned out that I had Gastrin - the stuff that makes your stomach produce acid - was about 300 times above average for a human being.

Episode 40:
Symptom Management Update
Transcript

So, basically, I had a gastrinoma, and we went from there.

You know, the treatment sequence was they did an embolization, which caused me to go into carcinoid crisis, and I ended up in intensive care, almost dying. My blood pressure was like 75 over 30, and my heart rate was like at around 35, and they actually told my wife I might not come out of it... but I did, obviously... although, the embolization itself worked for four months, five months, and then everything got worse.

And then I demanded... I had to go see other specialists to get a recommendation for surgery, and I was able to get that, which they took half my liver, to get that one out. There were actually still are four lesions, small lesions, in the other half of my liver. Ever since then, whenever I go to... I've had several surgeries and I have to always make sure there's someone there who understands about the crisis and is ready to treat it with the proper thing, and it's worked out okay. I just had PRRT last year. So, it's been a long road... (laughs) you know.

Up until now, we've been talking almost exclusively about carcinoid syndrome, which is caused by an excess of the hormone serotonin. But serotonin is only one of many hormones that can be produced by NENs. There are many kinds of functional NENs that can arise, and each comes with its own array of symptoms.

Soares: *The most classical ones we see in the pancreas. So, if someone has a tumor that is secreting the hormone insulin, then patients will present with low blood sugars - what's called hypoglycemia.*

Dillon: *With mildly low blood sugar, people feel very uncomfortable and sweaty and shaky, but with a severe episodes of low blood sugar they can pass out and have seizures, and it can get worse than that.*

Soares: *Another example of a tumor that one can have in the pancreas and give you a specific symptoms are what's called Glucagonoma, when patients will secrete Glucagon.*

Episode 40:
Symptom Management Update
Transcript

Dillon: *Glucagon is a natural hormone within the body that's truly an antagonist to the effect of insulin. So, insulin lowers blood sugars, glucagon raises blood sugars. And those two hormones are in a dynamic balance within the body. In normal circumstances, if the glucagon level goes up the effect of insulin is decreased within the body and the blood sugar will tend to... tend to rise.*

Soares: *And the typical presentation is related to patients that have poorly controlled blood sugars because of diabetes, low appetite, and weight loss, with skull cachexia and some skin lesions.*

Wolin: *And you could have what is called an atypical carcinoid syndrome, an unusual sort of thing, made by histamine-releasing tumors. And these cause a redness that doesn't just last for a few minutes, but can last for maybe half an hour. It also can cause diarrhea.*

Dillon: *Histamine, obviously, is the hormone that we think about, or the chemical that we think about, when we're talking about allergies. And patients can have hives, for example, and other allergic features with histamine.*

Wolin: *The flush is often bright red. The flushing often lasts long enough that it can lead to rosacea, where you have permanent redness of your face and nose just from the blood vessels in that area being dilated. And you can treat with anti-histamines as well as with somatostatin analogs. It's a special kind of syndrome.*

Dillon: *Any of these neuroendocrine tumors, but I find it particularly in neuroendocrine tumors associated with the pancreas or the lung, can produce hormones that can cause a person to secondarily produce an excessive amount of cortisol, so they actually get a syndrome called Cushing's syndrome.*

Wolin: *Cushing's syndrome is what happens if you have too much cortisone in your body - it's like overdoing prednisone for years and becoming very bloated, and having edema, and facial swelling, weight gain, and diabetes, and*

Episode 40:
Symptom Management Update
Transcript

breakdown of the bones. Lots of bad things could happen from too much steroid hormone being made as a result of ACTH production by the tumor - Adrenocorticotrophic Hormone - which stimulates the adrenal glands to manufacture cortisol. So, in this condition, the twenty-four-hour urinary cortisol is elevated, ACTH measurement in the blood is high, and it can be really a very serious problem.

There are also gastrinomas that produce gastrin, and V.I.P.-omas - or vipomas - that produce something called "vasoactive intestinal polypeptide" and other more rare functional NENs.

All of these kinds of tumors produce their own set of symptoms and have their own treatment protocols.

Still, with the majority of functional NENs, doctors reach for somatostatin analogs - octreotide and lanreotide - which seem to have the ability to regulate a variety of hormonal symptoms.

Liu: *Now, when it comes to our neuroendocrine world, when in the treatment of these types of things, the one thing is we're very, very fortunate, put it that way, in that the body in mother nature has created a system in which we can actually shut down a lot of the hormones just with one... almost just one molecule. It's somatostatin.*

So, somatostatin analogs are incredibly, incredibly powerful tools, because they do things that we probably don't even know about. And so, think of it this way - the analogy I always use is think of the somatostatin analog as a wet blanket. Fine. So, you take a big wet blanket and you throw it on the fire and you get out the fire mostly, and you can probably put a bunch of the embers that are kind of on the side, and that's kind of how a somatostatin analog works, it just kind of suppresses and depresses the whole endocrine system.

So when that happens... I mean despite the side, it is incredibly safe and incredibly well tolerated. It does help a lot of people because it helps dampen all of this endocrine aspect that we couldn't... I mean, just imagine if we had to pick a drug for every single hormone you had to

Episode 40:
Symptom Management Update
Transcript

block, it would probably be very complicated, and people would have a hard time taking enough medicine to probably keep it covered, but because of somatostatin analog works so well, you can actually cover a lot of things with one fell swoop.

Although there are several effective treatment options for functional NENs, there's still a lot we don't know about how NENs affect the hormonal system.

Liu: *The hormones we measure are what... maybe, like, seven, out of hundreds and hundreds of hormones and hormone fragments that the body produces? And how it's secreted, and how it's regulated, and where it goes, and what its receptors are, and stuff like that... it's extremely complicated, and we don't have the right tests for it. And so, we have people frequently - very, very frequently - who have this kind of carcinoid syndrome, they get the flushing, they get diarrhea, and then their serotonins (sic) are relatively normal. They're, like, not that off. So, in fact, we think that a lot of the serotonin story is not actually all there. So it's probably not totally 100% clear that serotonin is the only culprit. Don't get me wrong - it definitely contributes to it. It's definitely an aspect to it. It definitely causes morbidity, but it's probably much more complicated than we think.*

Dillion: *The process that regulates the release of hormones is complicated and it's diverse. Every other cell or gland that produces hormones in the body is regulated by another hormone from somewhere else, or another nerve supply from somewhere else.*

The treatment of these NEN-related hormonal symptoms is only going to improve as our understanding of these complex and subtle systems continues to grow.

Thanks for listening to NETwise. I'm Jessica Thomas, Director of Patient Education at NETRF.

Episode 40:
Symptom Management Update
Transcript

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Special thanks to everyone we interviewed for this episode. We are grateful for your expertise.

And we want to note that Cy Ball, whose story we heard, died in 2021. We appreciate that he shared his story with us.

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