

You can find information about subscribing to this series at netrf.org/podcast, where you'll also find a bunch of helpful charts, graphs, and videos that expand on this material.

Do you have a story to tell about your own NET journey? If you're a NET patient who would like to participate in a future episode, please email us and let us know! This month, we're particularly interested in speaking to people who have participated in a clinical trial as a part of their treatment, and also NET patients who were diagnosed and treated as an adolescent or young adult. If that sounds like you, drop us an email to podcast@netrf.org

Welcome to NET Wise. This is a podcast for neuroendocrine cancer patients and caregivers that presents expert information and patient perspectives. My name is Laran Hyder, from the Neuroendocrine Tumor Research Foundation.

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

The hormonal symptoms of NETs are caused by unique characteristics of the cells these tumors grow from. Here's Dr. Joseph Dillon, an endocrinologist and Medical Director of the Neuroendocrine Tumor Clinic at the University of Iowa:

Dillon: "These neuroendocrine cells, which constitute about one in every thousand cells within, say, the lung or within the intestine, are thought to be sensing the chemical environment in those organs, and they are then producing chemicals which they push out to the cells that are surrounding them, which then essentially tell the cells around them to work harder, work less hard, to absorb more nutrients in the bowel or absorb less nutrients in the bowel, et cetera."

These chemicals are known as hormones.

Dillon: "So hormones are chemical molecules that are made by hormone producing glands or cells within the body. They circulate around in the bloodstream and they activate certain processes elsewhere in the body. 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."

And because neuroendocrine cells can produce hormones, some NETs are capable of producing floods of unwanted and unneeded hormones, which can have all kinds of effects on your 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."

Some NETs produce hormones that throw our internal systems out of balance to such a degree that they can cause unwanted symptoms. These are referred to as "functional" NETs. Others do not necessarily produce an excess of hormones or cause symptoms; we term these as "non-functional" NETs.

It's important to recognize, just because a NET is considered non-functional does NOT necessarily mean that it isn't producing hormones - it might also mean that the hormones it produces are not causing a patient to experience identifiable symptoms. Here's Dr. David Metz, a gastroenterologist from the University of Pennsylvania:

Metz: "So nonfunctional neuroendocrine tumors may secrete products that don't cause hormonal symptoms."

Dillon: "Either they're producing the hormones but not producing enough of them, so that the patient does not feel any of the symptoms, or for some reason that patient is not particularly sensitive to those hormones, or the tumors are producing hormones which simply don't have very evident symptoms associated with them."

Metz: "For example, Chromogranin A, Pancreatic Polypeptide... we measure those as markers, but those products - which are at a higher level than what you'd expect in the normal blood - don't cause a symptom. You'll just have a blood level of Chromogranin A, that's 196 instead of 23, which is the normal range, but doesn't do anything to you. Whereas functional neuroendocrine tumors produce products that do cause functional effects.

Functional NETs - the ones that do cause hormonal symptoms - are often identified by the name of the hormone they most strongly produce. For example, some functional pancreatic NETs or pNETs like somatostatinomas, produce the hormone somatostatin, insulinomas produce insulin.

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. Insulinoma make you get a low glucose level. PTHRP-producing tumors, release a parathyroid hormone-like product that rise raises your calcium in the blood."

Here's Dr. Michelle Kang-Kim, an oncologist and researcher at Mt. Sinai Hospital in New York City:

Kang-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."

Keep in mind, though, that a single NET can produce more than one hormone at a time, and therefore might be causing a combination of different kinds of symptoms.

Kang-Kim: *"Some neuroendocrine tumors will oversecrete more than one hormone. So, although there's usually sort of a dominant hormone that is involved in any particular neuroendocrine tumor, we do see that sometimes there can be hormones that are co-secreted."*

Probably the most common and well-known of these NET-related hormonal conditions is carcinoid syndrome, which is caused by an excess of serotonin.

Creamer: *"So carcinoid syndrome is kind of the constellation of symptoms that is created by serotonin-secreting tumors. These are primarily in the small bowel, but you can also get carcinoid syndrome from lung primaries and some of the even less common primaries in the reproductive organs. But most commonly it's small bowel."*

Here's Dr. Aman Chauhan, an oncologist at the Markey Cancer Center at the University of Kentucky, followed by Dr. Eric Liu, a surgeon at the Rocky Mountain Cancer Center in Denver:

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."

Liu: "You have a tumor, right? It's spread around your body, mostly the liver, and then it secretes the serotonin in an unregulated way, and so when you get all this serotonin that's pouring out, it can cause a lot of problems."

Creamer: "So we see a lot of these patients, the main symptoms they experience are flushing - So they get the sensation of being very hot and especially in the face and chest, and then they often kind of get a red kind of rash that overcomes their face and chest."

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.'"

Of course, carcinoid syndrome is certainly not the only cause for someone to flush red. Menopause, for example, also causes skin flushing. To a trained observer, though, carcinoid flushing and menopausal flushing can often look different.

Kang-Kim: *"Certainly not 100% type of thing that you can use to distinguish them (sic), 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's 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 much more challenging symptom 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."*

Liu: "And we don't think about it but, you know, the tumor never sleeps, so that means the diarrhea never sleeps, so that means the patient never sleeps."

Flushing and diarrhea are two common, hallmark symptoms of Carcinoid Syndrome, but others 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 roughly 50% of patients with carcinoid syndrome, carcinoid heart disease is a major concern.

Liu: "One of the odd complications that can happen with carcinoid syndrome is something called carcinoid heart disease. 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. So when people have this complication, this carcinoid heart disease, their blood can literally flow backwards, and let me tell you, that is not good for anyone's health.

But that's an odd complication then 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.

Serotonin occurs widely throughout the body, influencing a variety of bodily and psychological functions. Not only does excess serotonin create some of the classic features of carcinoid syndrome, some doctors and patients report certain emotional effects.

Liu: *"The emotional aspects of carcinoid syndrome are not that well documented, but they absolutely 100% exist. 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.'"*

There is a lack of significant research on this topic, though. Excess serotonin could be associated with certain psychological effects. However, the extent of those effects and their relation to mood disorders is unclear.

Chauhan: *"There has (sic) been some studies looking specifically into (the) role of elevated serotonin in neuroendocrine tumor patients and can that cause mood issues. If I recall correctly, there was a study from Boston - Mass. General - and they basically concluded that*

the serotonin produced by a neuroendocrine tumor really does not cross the blood/brain barrier and goes to the CNS and affects mood. I can attest to it clinically, as well. I do not see mood disorders associated with carcinoid syndrome. I think the serotonin production by (a) neuroendocrine tumor does not really affect CNS and henceforth mood disorders."

Carcinoid syndrome mostly occurs in people with small bowel NETs, and often after they 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."*

And one exception to this is in women who have metastases in the ovaries.

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 illium 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."

The usual first-line treatment for carcinoid syndrome is a somatostatin analog like Octreotide or Lanreotide. In fact, treating carcinoid syndrome was the very first thing these drugs were approved and used for, before clinical trials also demonstrated their ability to manage tumor growth in some patients.

Dillon: *"In the context of carcinoid syndrome, by taking a medication such as Octreotide or Lanreotide, one would expect that there would be a decrease in hormone production by the tumor, and thus a decrease in the flushing and the diarrhea and those other components of the carcinoid syndrome. So that certainly is the first medication that we would think about, in terms of decreasing symptoms of carcinoid syndrome."*

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 recently approved drug used to manage carcinoid syndrome is called Telotristat.

Wolin: *“Telotristat, which goes by the brand name Xermelo - this is a drug which blocks the production of serotonin. There's an enzyme we called tryptophan hydroxylase, the turns the amino acid we eat in our diet, tryptophan, 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 analogues control that by blocking 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 than this is something that we can add on to therapy and patients have done very well with it.

We don't put anyone on Xermelo that doesn't have proven elevated serotonin levels, because if they don't have elevated serotonin then that's not what's causing their diarrhea. So we... patients with other primaries that are not serotonin-producing should not necessarily be getting this drug, that's not what it's meant for.

I would say it's typically well tolerated. Constipation, or really severe constipation - obstipation - can be a problem, and then, kind of, the side effects of constipation, so abdominal pain is one."

Removing or reducing the size of the tumor may also help to alleviate carcinoid syndrome related symptoms.

Dillon: *There are other ways to combat carcinoid syndrome, 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.*

And even things like nutritional supplements can also play an important role.

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. It also seems to reduce diarrhea in the early studies shows that that's the case with carcinoid tumors. A study that was done at university of Kentucky. So we're trying to make a large study to try to conclusively prove this and figure out how Enterade might figure into the treatment of carcinoid syndrome, but it's certainly quite nontoxic and quite exciting."

We have a lot of treatment options for NETs and hormonal symptoms, but frustratingly, it can sometimes take patients a long time to start receiving them, because time to accurate diagnosis can be lengthy. 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.”

Dillon: *“Patients are realizing that they're having these quite abnormal and troublesome symptoms, which can go on for more than five years, and yet their physicians are unable to come up with a definitive diagnosis.”*

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 your life has changed.”

Soares: "Thankfully, the awareness about neuroendocrine tumors is increasing, and we are spreading the word about thinking about neuroendocrine tumors in the differential, especially when patients are seeing a primary care physician or a gastroenterologist. 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 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're 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."

Nakakura: "I've had a few patients where we've started the surgery and just when the patient is put to sleep, the blood pressure plummets, and there's no blood pressure, and we're doing CPR and dramatically trying to resuscitate... bringing the patient back to life, essentially. And in a handful of cases where that's happened, we've actually stopped the surgery and deemed that surgery is not safe in this patient."

Liu: "And so every time we do an operation in patient with neuroendocrine, there is literally always a large bottle of Octreotide sitting on the anesthesiologist's desk, because if anything goes wrong, we can open that up right away and then we can treat the patient quickly and get things under control."

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. 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."

Serotonin is only one of many hormones that can be produced by NETs, and there are many other less common syndromes caused by functional NETs.

Dillon: *"A variety of hormones called 'kinins' or 'tachykinins', producing the flushing..."*

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 analogues. It's a special kind of syndrome."

But this is just the beginning. There is an entire galaxy of different hormonal symptoms, or conditions, that can be caused or exacerbated by functional NETs.

Soares: *"There are other types of functional tumor types. 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."*

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."

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 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 - Adrenocorticotropic 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 gastrinomas that produce gastrin, and V.I.P.-omas - or vipomas - that produced something called "vasoactive intestinal polypeptide", and other more rare functional NETs, all of which produce their own set of symptoms and have their own treatment protocols.

Interestingly, though, the first treatments doctors reach for in dealing with almost all of these conditions are the Somatostatin Analogs - Octreotide and Lanreotide - which seem to have the ability to regulate a huge variety of hormonal symptoms, many of which we don't really understand.

***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 analogues 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 analogue 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 analogue 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 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."

And honestly, there's still a lot we don't know about how NETs affect the hormonal system. Even the more well-understood syndromes are tremendously complicated, involving many different hormones that we know about and probably many, many more that we don't yet have any way to track.

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 serotonin (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.”

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

Thanks for listening to NET Wise. If you like the show and find it helpful, please leave a review on whatever app you're using to listen to it, and we'd also love to get your feedback at podcast@netrf.org.

My name is Laran Hyder. I'm the Director of Education and Outreach for the Neuroendocrine Tumor Research Foundation and the Executive Producer of this series. It was produced by David Hoffman of CitizenRacecar.

This episode is made possible by the generous support of Advanced Accelerator Applications - a Novartis Company, Lexicon Pharmaceuticals, Ipsen, and the Vincent E. Taylor Patient Education Fund.

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

This is a production of the Neuroendocrine Tumor Research Foundation, where we're committed to improving the lives of

patients, families, and caregivers affected by neuroendocrine cancer by funding research to discover cures and more effective treatments, and providing information and educational resources. Please visit us at [NETRF.org](https://www.netrf.org).

This podcast is not intended as, and shall not be relied upon as, medical advice. The Neuroendocrine Tumor Research Foundation encourages all users to verify any scientific information found here with their personal oncologist, physician, and/or appropriate qualified health professional. Listening to this podcast does not constitute a patient-physician relationship. The Neuroendocrine Tumor Research Foundation does not represent that any information provided here should supplant the reasoned, informed advice of a patient's personal oncologist, physician, or appropriate qualified health professional.