Episode 20 - "Gastric NET, Gastrinomas, Zollinger-Ellison Syndrome (ZES)" with Dr. David C. Metz
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Lisa Yen:

Welcome to the LACNETS podcast. I'm your host, Lisa Yen. I'm the LACNETS, Director of Programs and Outreach, as well as a caregiver and advocate for my husband who is living with NET. In each podcast episode, we talk to a NET expert who answers your top 10 questions. This podcast is for educational purposes only and does not constitute medical advice. Please discuss your questions and concerns with your physician.

Lisa Yen:

Welcome back to the LACNETS podcast. We're really excited to introduce today, Dr. David Metz who's joined us in the past in our second episode of the LACNETS podcast. So let me just tell you a little bit about Dr. Metz. He arrived at Penn Medicine in 1993, and he held a variety of leadership roles within the Department of Gastroenterology including Co-Directorship of the Neuroendocrine Tumor Center and the Penn NET treatment program. And Dr. Metz was previously a staff fellow at the National Institutes of Health, where he performed basic research in pancreatic acinar cell secretion and clinical research in Zollinger-Ellison syndrome. While at Penn Medicine, he served as the Chair of the North American Neuroendocrine Tumor Society (NANETS), as a member of the Liaison Committee for Recertification of the American Board of Internal Medicine, and on the Food and Drug Administration Gastrointestinal Drugs Advisory Committee, among other positions.

Dr. Metz's clinical interests at Penn included Zollinger-Ellison syndrome and other acid-peptic conditions, H. pylori infection, non-steroidal anti-inflammatory drug gastropathy and the diagnosis and management of patients with functional and non-functional neuroendocrine tumors of the pancreas and GI tract. He's been an investigator for several prominent clinical

trials, and he's published more than 200 articles that are now useful to us in clinical practice. He retired in July 2021 after 28 years at Penn Medicine and now lives in Southern California. He was recently honored by NANETS with a lifetime achievement award as well.

We've had the pleasure of having Dr. Metz join us in our LACNETS community and he's the reason we started the LACNETS podcast as we recorded one of our first episodes with Dr. Metz on the topic of diarrhea. We're really pleased to welcome him back to the LACNETS podcast with an episode on topics he's very well versed in that may not be commonly covered in NET patient education programs.

One other thing I want to say about Dr. Metz is that I really love that he coined the phrase NETologists" to describe a NET expert. So, Dr. Metz, welcome, and I'd love for you to share what got you interested in that patients and how you coined that phrase "NETologists?"

Dr Metz:

Well, Hi, Lisa. I actually called myself a neuroendocrinologist. But NETologists would work the same way. I think the reason that that term is somewhat important, tongue in cheek, is that it's really reflective of the multi-specialty nature of the neuroendocrinology care. You can come at neuroendocrinology from gastrointestinal side or the endocrinology side or a surgical side or oncology, of course, pathology. But ultimately, to be a neuroendocrinologist, you need to be able to join all of those subspecialties together, and it's a subspecialty of its own making. So hence the term neuroendocrinologist. I started as a, as you mentioned, at the NIH, doing my fellowship and the lab was clinically focused at that time on Zollinger-Ellison syndrome, which is a rare neuroendocrine tumor. Not that rare in that it is the second most common and functional neuroendocrine tumor and the most common functional tumor of the pancreas, together with insulinoma. Obviously, carcinoid syndrome being the most common one. But there's a gastrointestinal division, we were studying Zollinger Ellison syndrome, given its association with peptic ulcer disease. And that sort of led me into the world of neuroendocrinology.

Lisa Yen:

Well, thank you so much for that clarification and for becoming a neuroendocrinologist and specifically in this area of gastric NET, Zollinger Ellison syndrome, an area that there probably wasn't a lot of attention to beforehand. We're really grateful to you.

Dr Metz:

Cool.

Lisa Yen:

Well, how about we jump into the 10 questions?

Dr Metz:

Do it.

Lisa Yen:

Okay. The first question is, what is gastric NET? And how is it found? Furthermore, what are the symptoms and how is it different from stomach cancer or other types of NETs?

Dr Metz:

So, one needs to recognize that neuroendocrine tumors or neuroendocrine neoplasms, as people like to talk about them nowadays, can occur anywhere in the body at all. The biggest site of course being the gastrointestinal tract, but that starts at the lips and ends at the anus and includes a whole lot of different organs, including the appendages, the liver, where the metastases go, and the pancreas where they are lots of other primary tumors. So the GI NETS are widespread, but we've started recognizing that there is a group of neuroendocrine tumors that tend to be smaller and maybe less recognized by oncology and more recognized by gastroenterologist. And those would be the smaller tumors that occur in the stomach, the duodenum, and the rectum, primarily.

Now, the gastric neuroendocrine tumors or gastric carcinoids, as they're also called, themselves can be subdivided into a variety of different types. And we generally talk about three gastric carcinoid tumors or gastric neuroendocrine tumors: type one, type two, and type three. There are potentially others and we are also seeing some new kinds that are related to treatment with anti-secretory agents.

But traditionally speaking, type 1 and type 2 gastric carcinoids arise from ECL cells in the stomach: enterochromaffin-like cells. And type 3 is a different kind of tumor that arises from an EC cell, an enterochromaffin cell. And those terms are pathologic terms based on staining that can be done on biopsies with or without taking up silver or girofle, people talk about.

The type 1 and 2 carcinoids, as I mentioned, come from ECL cells. And ECL cells, traditionally, have only really been well recognized in terms of how the acid secretion profiles develop in humans. So in order to make acid in the stomach, you have a parietal cell that is the acid-making factory, but that parietal cell responds to hormones that are released by ECL cells, primarily a hormone called histamine or gastrin, another hormone that's released from G cells—G cells being another neuroendocrine tumor in the antrum, bottom end of the stomach. That histamine is the major driver for the parietal cell to make acid. And to stimulate histamine, the gastrin from these G cells, in addition to driving parietal cells, drives the ECL cell. So a high level of gastrin for a prolonged period of time will lead to an enlargement of the ECL cell mass and you could call them "*ECLomas*," or *tumors of ECL cells*. And those ECL cells really are what are ultimately type 1 and type 2 gastric carcinoids.

Type 1 gastric carcinoids being in response to an absence of acid. So that is a disease called *atrophic gastritis*, or other people recognize it as *pernicious anemia* because the parietal cells make intrinsic factor that is important for absorption of B12. And if you don't have any parietal cells, not only don't you make acid, but you can't absorb B12 and so you get pernicious anemia. In the absence of the acid, the body makes a high gastrin. That gastrin drives both the ECL cells and the parietal cells, but no acid results and from driving the ECL cells, you get what are called type 1 carcinoids. These are usually multiple, and as I say associated with B12 deficiency and an absence of acid. They are the most common type of gastric carcinoids. They grow slowly. And they usually are not very aggressive and can be managed often without any major big interventions, although the most important thing is to go onto B12 replacement.

Now whether a similar kind of carcinoid can be caused by long-dosing, anti-secretory therapies with proton pump inhibitors is kind of controversial at the moment. That's a very rare issue. And I don't want people listening to this podcast to get anxious about taking the PPIs if they need them. Because even if that is an issue, it takes 20 plus years and it's not a big concern, and that may be variation on that type of carcinoid.

Type 2 carcinoid also result from hypergastric anemia, high gastrin levels, driving the G cells to make gastrin to drive the ECLs to make ECLomas. They only seem to occur in hypergastrinemia associated with multiple endocrine neoplasia type 1, which is a rare hereditary disease. And whether this is associated with other kinds of hypergastrinemia, such as in Zollinger-Ellison [Z-E] syndrome, of a sporadic nature is possible, but again hasn't been really defined very well. But Zollinger-Ellison syndrome, which I'm sure we'll get onto talk in a little while, is a neuroendocrine tumor that occurs in the pancreas or duodenum. That's called a *true gastrinoma* because that is a tumor that makes gastrin. And that gastrin drives the ECL cells to drive the parietal cells which are now present in this disease to make a whole lot of acid. So that is the prototypical hypersecretory disease in which high gastrin drive ECL cells and drive the parietal cell to make acid with Z-E.

And in the hereditary component, the hereditary type of Zollinger Ellison syndrome that associated with MEN1, people do occasionally get type 2 gastric carcinoids, which are ECLomas in a different setting. Not as common by far as type 1s, and probably not a major concern because in that situation, what you're really more concerned of is getting rid of the source of the gastrin, which is malignant neuroendocrine production. In the type one, as I'm saying, it's a response to the absence, so it's a physiologic response.

Type 3 gastric carcinoma are very rare, and they tend to occur from a different kind of neuroendocrine cell in the stomach. They are highly aggressive. They generally are grade 2 or even grade 3, and that really should be considered a gastric cancer type situation and as treated as an aggressive malignancy, whereas type ones are much more benign. And type 2 sort of fit in between. The type 3s, although they are the rarest, are the ones to be most concerned about.

Now how do these tumors differ from gastric cancer? Atrophy, or absence of parietal cells, is a prerequisite for the development of gastric cancer. And just like there is a sequence with colon polyps going from benign to more aggressive to adenomas to higher grade adenomas to cancers. The same thing will occur in the stomach. It's a cascade called the "*Correa cascade*" after a very well-known pathologist on the East Coast. And what develops there is you get absence of parietal cells replaced by normal intestinal-type cells that are trying to restore acid secretion, but they are unable to do that. And that's called *intestinal metaplasia*. That then degenerates to intestinal dysplasia, and that dysplasia develops an adenocarcinoma. So that is a cancer that develops from a normal lining cell as opposed to a neuroendocrine cell. And the major association in gastric cancer is with Helicobacter pylori [H. Pylori] infection. and H. pylori gastritis can lead after many, many years to atrophy and produce this cancer.

Now, you ask me if type 1 is associated with atrophy. Why aren't they associated with gastric cancer? And actually, they are associated with gastric cancers but a much lower likelihood then with H. pylori infection. And so, the reason to really survey people with type 1 gastric carcinoids is more to make sure they don't develop dysplasia and gastric cancer and to look at the tumors unless they get big, in which case, you would want to remove them.

And another form of gastric cancer I just want to mention is the hereditary forms of gastric cancer, which is an *E-cadherin* abnormality based on genetics, in which you inherit a predisposition to developing gastric cancer. And those patients with that genetic disorder probably should have prophylactic gastrectomies early on in life because the likelihood of developing cancer in that situation is very, very high.

Lisa Yen:
Wow, thank you for this excellent, very informative overview of gastric NET and how it compares to gastric cancer. I'm curious, how is it found? How's this gastric NET found? And what are the types of symptoms that people might experience?

Dr Metz:

One of the more common lesions for lumps and bumps in the stomach is a condition called *fundic gland polyps, FTPS*. And fundic gland polyps [are] sort of thought of as being obstructed parietal cells that develop swelling and cause small little polyps. And we're starting to see these more and more now, in patients who take proton pump inhibitors. They tend to be benign most of the time. If they're associated with a rare disease called *familial adenomatous polyposis*, which is a colon cancer disease. Sometimes if the fundic gland polyps can be of more concern, but generally speaking, they're benign, lumpy, bumpy things. And many people who get an endoscopy for any reason, just because they have belly pain or because they're getting heartburn and getting scoped to make sure they don't have Barrett's esophagus or esophagitis. The doc sees a little lumpy bumpy stuff in the stomach, and they take a biopsy and "Oh my God, it's a type 1 carcinoid."

As I've already suggested that "Oh my God" is not such a worrisome "Oh my God," because the type 1 carcinoids really tend to be much more benignly behaving conditions. But that's one way that most of these patients are identified. And obviously people are getting upper endoscopy is for lots of reasons.

Of course, if you develop an anemia and you end up going to hematologist and they find out that you have vitamin B12 deficiency, then you have to work out, is it a B12 deficiency because you can't absorb B 12 because you don't make intrinsic factor? Aha! Atrophy gastritis and pernicious anemia? Or is it a B12 deficiency because of many other causes of diseases in the pancreas, diseases in the small bowel, or even people who are vegan and don't have B12 orally enough to get any oral absorption?

So those are the two major ways that one would come up identifying atrophic gastritis. Of course, Helicobacter pylori infection is ubiquitous in the world. It's, in fact, I think the most common infection worldwide, and half of the population of the world has it much more in developing countries than in the United States where the incidence is a lot lower. But people who get abdominal pain and peptic ulcers, we know H. pylori is very predominant in the cause, in addition to nonsteroidal anti-inflammatory drugs, that people get upper endoscopy is looking for ulcers, and they may find H. Pylori. And that's another reason you would find atrophy. That for some reason, as I mentioned earlier, we don't quite understand why the H. Pylori patients are more predisposed to getting atrophy and gastric cancer, whereas the pernicious anemia atrophic patients are more likely to get B12 deficiency and type 1 gastric carcinoids.

Lisa Yen:

Thank you, it's good to know what the associations are. So now that someone's had a diagnosis, or once someone's had a diagnosis, how does gastric NET treat it and then how is it monitored?

Dr Metz:

So, let's start to the type threes. The type 3s, as I said, are much more concerning. And for any patients who have those, they will present with larger lesions, and they could be anywhere in the stomach. And they are more often associated with bleeding and anemia and pain. And that should be treated as a gastric cancer. So that requires a resection. And the same sort of approaches as any higher grade neuroendocrine tumors, including gallium scanning, and surveillance after treatment.

Type 2s are very rare. And for some reason, as I mentioned, supposedly only associated with MEN1-type gastrinoma as opposed to sporadic gastrinomas. Although I think that that's probably not true. And if you had a Z-E sporadic tumor that lasted long enough, I think it's possible. In those sort of situations, especially the MEN patients who have neuroendocrine tumors that develop in the pancreas that are functional and nonfunctional and probably are of more concern, they also get neuroendocrine tumors in the lung, neuroendocrine tumors in the thymus. And so, in that situation, although you may find a type 2 gastrinoma, you really tend to

be far more concerned about treating the MEN, and the Z-E, and the whole patient. And that becomes just part of the concert.

Type 1s, as I've mentioned, tend to be relatively benign. The standard of care is that anything over two centimeters in size, and those tend to be rare, should be removed endoscopically. And if they're six or less, you should remove them all endoscopically and then survey the patient frequently. Most patients with type 1 carcinoids, however, have multiple. And they can have 50, 60, 70, or 100. And it looks very different from person to person. Some just look like a flat mucosa with a couple of lumpy, bumpy things. And some look like a nodularity filling up the whole stomach. So, it really does need to be individualized. You could cure type ones, if you removed all the gastrin production. So, if you took out the antrum of the stomach where the G cells are, you would lose the hypergastrinemia, and the tumors would go away. That, however, is a difficult way to live and is probably overkill in 99% of patients.

Similarly, you could remove the fundus of the stomach, you could take out all the acid-secretory components of the stomach where all these ECL cells are. And if you did a fundectomy you would get rid of all the tumors. But once again, from a morbidity perspective, that's a tough thing to go through. So we tend not in the modern era to do any types of resection except under certain selected kind of cases. And before one would even do that as I would consider an anti-secretory approach by using a somatostatin analog which could switch off the gastrin and stop the ECL cells. That of course means it's a lifelong commitment, which to your audience, is something they understand well. But again, you have the issues associated with pancreatic insufficiency and diabetes and gallstones. And so, most persons with pernicious anemia, the bottom line is replace the B12, take out the larger lesions endoscopically, and follow them at intervals. And only really get aggressive if it looks like things need to have that kind of approach.

Lisa Yen:

Thank you for that. That's really helpful to break it all down, especially to the type of NET. And when you say with the type 1 that they would need surveillance frequently, how frequently with the endoscopies need to be?

Dr Metz:

Well, the reason I said frequently didn't give you a number is that there is no real agreement as to this. So, in the United States, the standard of care is not to survey at all. The Europeans like to survey and the data in the absence of any dysplasia on biopsies. Remember, the real reason for surveying is to look for gastric cancer. If there's no dysplasia, the argument is somewhere around about three years, one to three years. Many docs however do survey patients more frequently than that. When I was practicing, we had a rather large group of patients with autoimmune gastritis and type 1 carcinoids. And I would survey them at roughly three yearly intervals as long as there was no dysplasia. There is a small incidence of progression. So, I think it really is important to survey but I don't really know the right number for that.

Lisa Yen:

Thanks for that clarification and who would survey them? Would it be their gastroenterologist?

Dr Metz:

Yeah, these small neuroendocrine tumors of the stomach, duodenum and colon generally should be treated and managed by gastroenterologist unless they have enough of a risk to be concerned for metastasis. And in that case, an oncologist would be brought into the fold and or at times, surgeons as well, obviously. But if you've got a type 1 pernicious anemia, and your blood cancers controlled and you're taking your B12, and you've looked for other autoimmune conditions that are associated, which I didn't mention yet. That B12 deficiency and pernicious anemia and atrophic gastritis and type 1 carcinoids is part of the autoimmune polyglandular group of diseases.

The next most important one to look for is hypothyroidism from Hashimotos thyroiditis, and those patients will need thyroid replacement. So, everybody who has type 1 gastric carcinoid should probably have their thyroid checked. And then there's a whole long list of autoimmune conditions that you could have that would be associated with this. But generally speaking, those are the two that are important. Addison's disease is a serious one that you don't want to miss but is very rare. Vitiligo is a skin condition with loss of pigmentation that in itself isn't terribly dangerous but can be disfiguring. And then there's a whole long list of other autoimmunities that people may potentially have. But generally speaking, the type 1 carcinoids should be followed by gastroenterologist,

Lisa Yen:

Thank you. And thank you for that additional information about what other things to check, like the thyroid.
So, let's shift a little bit to gastrinoma. What is the gastrinoma and how and where is it found? Are gastrinomas and gastric NET the same thing?

Dr Metz:

No. So gastrinoma is a neuroendocrine tumor that makes gastrin and you can get a gastrinoma, anywhere you can get a neuroendocrine tumor. So I actually recall a patient who had a gastrinoma in the heart. I remember one patient when I was training, and it was difficult to remove those. And so, that patient was treated symptomatically, obviously.

But the term gastrinoma basically means that “OMA,” a neuroendocrine tumor that makes gastrin. So ECL cells wouldn't be gastrinomas because they respond to gastrin. But the G cell tumors in the antrum of the stomach, if they develop, could be a type of a gastrinoma, but would really be an H. Pylori associated atrophy condition. And they don't tend to get

macroscopic tumors. Although there was a time in the old days we would talk about type 2 Zollinger Ellison syndrome, which would be in theory, a gastrinoma arising in the antrum. But that's a rare location.

Most gastrinomas occur in the duodenal wall, or in the pancreas. And I think we're beginning to learn as time goes on that the duodenum is probably more of a common site than the pancreas. And the distinction needs to be made between a gastrinoma, in other words, a tumor that makes gastrin and Zollinger Ellison syndrome, which is a symptom complex as a consequence of high gastrin, which is due to a gastrinoma.

So, measuring the gastrin in the blood doesn't mean you've got a gastrinoma, in fact, you could be atrophic and have no acid production. Measuring a high gastrin in a patient who has symptoms of hypergastrinemia with excessive acid production, and peptic ulcer disease and diarrhea and abdominal pain and bleeding, that makes it Zollinger Ellison syndrome.

And the gastrinomas, as I've mentioned, could be in those two locations or anywhere else in the body. And as I've already alluded to with the MEN1 story, you get two kinds of gastrinomas. You get the MEN1-associated gastrinomas and the sporadic gastrinomas. MEN1 gastrinomas are about a third to a quarter of all the gastrinomas. And it's important in that setting to think about multiple endocrine neoplasia type one, MEN1 being a hereditary condition, and therefore, you need to screen family members. But more importantly in the individual who has MEN1 is to look for the other associated MEN associations. Most important being hyperparathyroidism, which causes excessive calcium in the blood, which is from foregland hyperplasia to be distinguished from just an adenoma in the parathyroids, which can also give you hypercalcemia. But this is the most common first presentation of MEN1 syndrome. Then MEN1 patients also get pancreatic neuroendocrine tumors or actually duodenal pancreatic neuroendocrine tumors. The most common one being a nonfunctional tumor, which we call a *PPoma* because it releases pancreatic polypeptide, but it doesn't cause any symptoms. And the PPomas can grow quite large and get malignant and metastasize and are often a big problem in MEN patients.

As far as functional tumors in the pancreas are concerned, MEN1 patients, the next two most common would be insulinomas and Zollinger-Ellison syndrome gastrinomas. Insulinomas, are usually single, they're almost always in the pancreas, they cause low sugar from high insulin. And in that situation, you need to try and remove that because it can be quite significantly morbid. The problem with MEN patients is how do you know which is the insulinoma and which is the PPoma and which is the Zollinger-Ellison gastrinoma and which is the glucagonoma and all the other omas that these patients can get. And it's very, very tricky, which is why you need an expert to look after it. We usually don't operate on MEN1-associated lesions unless they're two and a half centimeters in size, as opposed to sporadic neuroendocrine tumors where we would operate at a much lower size. And the reason for that is that because they get so many tumors in so many places, you end up potentially making it more of a morbid operation, without necessarily even curing them. And to that end, it's important to know that in Zollinger-

Ellison associated MEN1 syndrome, those gastrinomas tend to occur in the wall of the duodenum, and tend to be multiple in nature.

So the standard approach right now is if you get Z-E sporadic, and you've ruled out MEN1 syndrome, you try and operate because you can cure them about 40% of the time of the Z-E syndrome. But if they have MEN1 syndrome with multiple primaries, the chances are you're not going to be as good a result. And then you might end up after a Whipple operation with having a lot of morbidity and side effects. So it's very important to make that distinction. Of course, if you have the MEN1 disease, you also got to look for the other conditions, notably thymic neuroendocrine tumors or thymic carcinoids, which can be kind of serious, and also lung carcinoids in MEN1 patients and some of those can have the carcinoid syndrome associated with it. So MEN1 has a very widespread different kind of neuroendocrine disease that needs, again, multidisciplinary care.

Sporadic Zollinger Ellison syndrome is really a gastroenterologist condition. And then what you usually present with is going to be the symptoms of hypergastrinemia with an intact stomach. So consequently, overwhelming secretory diarrhea, which is similar to carcinoid syndrome diarrhea. Or other kinds of secretory diarrhea like VIPoma syndrome, another neuroendocrine tumor. Or abdominal pain from acid overproduction and peptic ulcer disease. Usually, the teachings are if you get multiple ulcers in unusual locations in a repeated patient, you need to think of Z-E as opposed to idiopathic peptic ulcer disease, which is primarily H. Pylori-associated or nonsteroidal-associated. But in the modern world with anti-secretory therapy, these patients are identified early on, go onto treatment early on, and it's actually very difficult to make the distinction. So one of the jobs of a gastroenterologist in a person with ulcers is to say, “Could this be the one in thousand that is a Z-E associated ulcer, as opposed to one of the other 999s in which they also could be from nonsteroidal agents or H. Pylori or very rarely other conditions.

So that's your best chance. You want to make sure you check the gastrin level as you diagnose the ulcer. Because once you've put them on to anti-secretory therapy, as we've already discussed with the way you get type 1 and 2 carcinoids of stomach, if you're on a PPI, you’re switching off acid production. The G cells say, “I don't see any acid, let's make some gastrin.” They make gastrin and they drive the ECL cells. The ECL cells supposed to make you acid, that that high gastrin and then, then be a response to the treatment as opposed to the actual cause of the ulcers. And so, the best time to try and rule out Z-E is the first time, as you make the diagnosis. And that's an important teaching point for gastroenterologists.

Lisa Yen:

That's really helpful. So, it's really important to check the gastrin level before going on a PPI.

Dr Metz:

Only if you've got symptoms of ulcer disease. The most common reason for a long-standing PPI treatment is for reflux disease, right? People with peptic ulcers get six weeks or so and in theory, they should stop. And that's a good reason why they should stop because if things recur, then you got to worry about other causes. But many people unfortunately get put on a PPI for nonspecific kind of discomfort. If you're getting a PPI for typical heartburn, although the patients do get heartburn 60% of the time, as opposed to the normal population about 15 to 20% of the time. But most people who get heartburn just because it's such a common condition don't have Z-E and so I don't think you should get a gastrin every time you start a PPI. But I think if you find an ulcer, yes, you should probably get a gastrin.

Lisa Yen:

Yeah, thanks for that clarification. So, with an ulcer, to check the gastrin level before starting a PPI. And one thing that really stands out about all that you're saying is that there are so many nuances to it. And it's really helpful to have all this information so that you can have an educated discussion, because as you said, some of these treatments, they're not nothing. It definitely affects people's quality of life.

Dr. Metz:

Absolutely. I mean, that's why I would say neuroendocrinology or NETology, as we've now decided, is a subspecialty in itself. And you can come at it as I said, as a gastroenterologist with these sort of nuanced discussions, not to belittle any of the nuanced discussions that come from being a nuclear medicine and working out how to use PRRT or an oncologist and deciding which VEGF inhibitors is better than which chemo agent. So even within the field of neuroendocrinology, you can be a sort of sub-sub-subspecialist to some extent. And I would say that it really is important, if you have these conditions to have somebody who's had some experience and understands these nuances.

Lisa Yen:

Yeah, thank you for that. And for clarifying a lot of this and giving us a little primer on MEN1 as well. So, you know, you've talked a lot about gastrinomas and various types. How is it treated? And I know you've kind of touched on the different types.

Dr. Metz:

Yeah, so what I would say is that gastrinomas, like any other functional neuroendocrine tumor, have two areas that need to be addressed. First is the functional nature of the tumor. And secondly is the tumor itself. Now in carcinoid syndrome, you address the functional nature of the tumor with an SSA and you address the tumor itself with an SSA. So, you might be using the same approach for both. And in actual fact, you could give an SSA to Z-E patients and they would have less gastrin production, and you may not necessarily treat the functional disease any differently. However, as we've discussed, the final common pathway of gastrin that causes

any disease is really via acid production and a good proton pump inhibitor switches have all the symptoms of Zollinger Ellison syndrome. That without worrying about diabetes and gallstones and pancreatic insufficiencies, you could control the syndrome with a PPI.

And the National Institutes of Health when I was doing my fellowship back many years back was looking at all the different kinds of anti-secretory drugs, the H2 antagonists and the proton pump inhibitors. And now there's a new potential drug that's going to become hopefully available in due course called a PCAB, which is being studied at this stage and is not available yet in the US, to switch off acid without necessarily having those other side effects. But in addition to controlling acid, you have to control the tumor. Controlling acid, we used to because peptic ulcer disease was so fulminant, and it was a cause of death in Z-E patients with bleeding. So commonly before the available of PPIs, H2 antagonists worked but you needed to use massive doses and go up every year on a dose. When we started with PPIs, we used very high doses and we caused in addition to the Z-E gastrin anemia, we would have secondary drug-induced type of anemia. And then we started worrying about is that an issue? Probably not. But nevertheless, many patients are overtreated.

I treat all the patients with twice daily PPIs. And the reason for that is, if you lose control of acid, you can develop ulcers and bleeding within 24 hours—massive bleeding, life threatening. So although these drugs work for 24 hours, if you take it twice today, and you forget a drug, or you get some diarrhea, or you have some vomiting, or for some reason that doesn't work, it is a much less likelihood of you getting into trouble and taking a drug twice a day is generally well tolerated. But you don't need the massive doses we used to use and probably a double dose of a PPI twice a day is fine in most patients. In the old days, we used to measure the actual acid production by putting a tube down and sucking up the juice and seeing how much acid was in the stomach at the end of the dosing interval. If you do what I'm suggesting double dose twice a day, you don't really need to do that much. But it's still somewhat controversial as to how much PPI is needed.

MEN patients tend to need more than sporadic Z-E patients. Not sure why. But once you've controlled the acid, that's just the beginning. Now, the next step is to say, “Do they have MEN1 or not?” So you then got to get the parathyroid levels checked because almost always hyperparathyroidism precedes, but not always. And you got to look for the other associations with MEN1 which requires imaging studies. And if so, potentially genetic studies in the family etc. And then the third issue, of course, whether they have MEN1 or not, is to address the tumors in MEN, there are multiple different kinds in different places. In sporadic Z-E, you got to try and prove it's sporadic. And if that's sporadic, the aim is to try and operate if possible because if you can remove the primary before they metastasize, there is about I would say a 40% cure rate surgically. Obviously, that doesn't happen in every case. And some tumors are in ugly places, like I mentioned, the patient with a tumor in the heart, very unusual. But you can often see duodenal primaries even in sporadic patients and sometimes it's difficult to do a Whipple operation for you know, a tiny six-millimeter lesion. And so sometimes we try other approaches to wedge resections, endoscopic resections. But the truth of the matter is, you really need to give them a shot at cure early on because if you miss that boat, which often

happens is you know, in neuroendocrinology, then you're dealing with a metastatic condition. And let me just say that if you've got a metastatic Z-E or a metastatic carcinoid or a metastatic glucagonoma or a metastatic VIPoma, I don't think necessarily other than controlling the hormonal syndrome with an SSA, your treatment should be that much different from if you have a non-functional tumor. And I don't know necessarily if we can say that the one type is more aggressive than another type. And I think it comes back down to the usual neuroendocrine approach of grade and stage rather than functionality or not.

Lisa Yen:

Wow, thanks for that thorough explanation. And so, you mentioned these high doses of PPI and you also alluded to maybe someone should come off. So, for people who need the PPI –MEN1 or Zollinger Ellison syndrome, how long are they on it? And is there a danger in taking proton pump inhibitors for a long time or in high doses?

Dr. Metz:

Okay, so proton pump inhibitors are spectacular drugs. When they are needed, they work beautifully, and there is very little to match them. I've mentioned the PCABS, which are still potentially coming. But right now, if you need a PPI, you should take a PPI. However, there are only certain conditions in which a PPI should be taken long-term. Peptic ulcer disease in itself is not a reason to take PPIs long term, unless it's associated with Z-E, because if you stop the PPI in that situation, you're going to get hypergastrinemia back and another ulcer. But in an H. Pylori-associated ulcer or a nonsteroidal-associated ulcer, once the ulcer has been appropriately healed and the non-steroidal has been stopped or the H. Pylori has been cured, you don't need to take your PPI forever any longer.

There are three reasons, as I said:
(1) Hypersecretory states like Zollinger-Ellison syndrome being the most important one.
(2) Nonsteroidal prophylaxis, people who need to take nons-teroidals for their arthritis every single day because otherwise they can't get out of bed in the morning.
(3) And reflux disease which has many different manifestations like just heartburn, or heartburn with esophagitis, or heartburn with Barrett's esophagus which is a pre-malignant condition. Any of those three conditions, you should be on a PPI at the lowest effective maintenance dose. We're going to get onto what that means. Unfortunately, there are people all over the world who end up on a PPI without proven reflux NSAID gastropathy or Zollinger Ellison syndrome and get it for dyspepsia, indigestion and “Oo, it makes me feel better, and I stay on it.” And those people probably don't need PPIs long term and probably shouldn't be on them long term. And they are now lots of writings about all the potential side effects of long-term PPIs. I have the dubious distinction of having written a paper many years ago and bone density issues which caused an absolute furor. The bottom line is if you’re an elderly person, especially a woman who's postmenopausal, whether you're on a PPI or not, you should have your bone density checked, and if it's low, it should be addressed. But PPIs have now been associated with that, with Alzheimer's, with renal disease, with bacterial overgrowth, with a whole slew of conditions

that are potentially associated, more likely just confounding, that I really find them spectacular and safe drugs. But if you don't need a PPI, you shouldn't be on one.

And what do I mean by lowest effective maintenance dose? I mean the following:

(1) If you take NSAIDs, and you're them because you need it, for NSAID prophylaxis, it's a once a day, half dose forever until you stop it, especially in people at risk. And the people at risk are those that have high dose NSAIDs, who are on an NSAID and another NSAID. And the usual one would be an NSAID for arthritis, and aspirin for cardiac disease. So, having the two of them is a risk. So if you're on an NSAID and you're over 70 years old, you potentially should be on it. Most patients who are young and taking NSAIDs because they hurt themselves playing pickleball, they don't need to stay on it forever, and they shouldn't be on a PPI.

(2) Reflux disease. If you have reflux associated with any endoscopic findings, in other words, Barrett's esophagus, or esophagitis, you should probably be on a once daily dose, half dose, maintenance. But if you're just having heartburn without erosions and without Barrett's esophagus, you should probably only be on a PPI as needed or at the lowest effective dose.

(3) If you have a hypersecretory condition, you need to be on a PPI every single day. And in Z-E, you need to be on a PPI in my personal opinion, twice a day. But that doesn't mean you need to be on massive doses. You can be on a full dose once or twice a day. Or in other words, a half dose twice a day or a full dose twice a day. And if you still having symptoms, and you can't distinguish that, the best thing for your doctor to do is to do an upper endoscopy in the last hour before the next dose of drug. So, it's usually an 8am endoscopy. And to suck some juice up out of the stomach. And if you're making acid at a significant amount on the endoscopy, you probably would need more drugs. And that's sort of a cheap man's way of doing what we used to do in the old days which was proper gastric analysis, and nobody really tends to do that much anymore. But most of the time, twice a day full dose is more than enough in most patients. Now, when you get to have widely metastatic disease and a massive, overwhelming amount of gastrin production by that stage, I think you're on SSA anyway which is going to help. And even so, if you end up being on a higher dose of PPI, the potential risks aren't enough for you to worry about it and I would say take it. So are PPIs bad for you? Minimally so. They are incredibly good drugs, but they should be used appropriately in people that need them. And at the right dose.

Lisa Yen:

Yeah, again, your very thorough answer shows the nuances and how individualized the care needs to be. So how is the gastrinoma monitored? How often would you recommend endoscopies or gastrin levels?

Dr. Metz:

So that's another good question because I think we used to overdo that a lot in the old days. You know, we used to scope patients every year. I don't know if you really need to have a scope every year. I think if you're asymptomatic, and you're on a good dose of drugs, you don't have diarrhea and you don’t have belly pain and you don't have heartburn and your gastrin is controlled. And remember the drugs themselves cause gastrin elevation.

So, what does the gastrin level mean if you're taking a drug that also increases the gastrin? So is the gastrin level predictive of progression of disease? Kind of controversial, but when you get up to massive levels of gastrin, I think it's probably is to some extent, but in that case, you're dealing with a metastatic neuroendocrine tumor, and you're talking about PRRT and other kinds of interventions. And so the gastrin just becomes a small factor. In early stages, people used to talk about gastrinomas having the highest level of gastrin. But that's actually not true, because true atrophy, if you don't make any acid at all, your gastrin level will be as high or higher than it is in earlier stages of Z-E. So, it doesn't really help. In the old days, we used to measure the actual acid production. The normal level in a man was 10 and in a woman was 5.6 at rest, and then we'd stimulate them with Pentagastrin, which is a pharmaceutical-type gastrin. And you would measure the BAO to MAO ratio, the *Basal Acid Output [BAO]* with a *Maximum Acid Ratio [MAO]*, and if it was greater than 0.7, it was a higher risk that it was going to be Z-E. You know, we don't tend to do that or need that anymore now with functional imaging and gallium scanning, you know, those sorts of things aren't being done again. So people tend not to measure gastric acid even diagnostically. And as far as maintenance is concerned, I suppose I wouldn't argue with an endoscopy once a year. And I wouldn't disagree with a gastrin and every now and then. But I think once the hormonal syndrome is taken out of the picture with therapy, you’re really dealing with how you would address any other neuroendocrine tumor, according to grade and stage.

Lisa Yen:

Yeah, thank you. So, you already touched a lot on gastrin levels. And I was going to ask you, if a high gastrin level means someone has a gastrinoma or are there other causes and you've touched on that. I also wanted to ask you can you have a high gastrin level without having a gastrinoma? And what are some other things that might cause false high gastrin level?

Dr. Metz:

Yeah, absolutely. As we've discussed, if the gastrin is produced by a tumor, and gives you high acid output, you're gonna have a gastrinoma causing Zollinger Ellison syndrome. But if you don't have the ability to make acid, either because you've got pernicious anemia, or end-stage H. pylori infection, or they are very rare genetic diseases in which the proton pumps themselves don't form properly, which has now been described as yet another potential way you can get a ECLoma and a type 1 carcinoid. Those patients will all have high gastrins as a response to try and restore acid, and that is going to therefore be a gastrin elevation without a tumor. If you don't have your gastrin level measured properly, you will easily have a high gastrin. Because every time you eat, you stretch the wall of the antrum. And you tell your G cells to make gastrin

so that you can make acid to digest the food that you've just put into your stomach. When that acid gets produced, it switches off the G-cell drive. However, if you then think of measuring a gastrin level in a patient who's not fasting, you're going to have high gastrin just by having not fasted, and that's probably the most common cause people come along with high gastrins, because that's what gastrin is for. It goes up if you eat. So nonfasting is probably the most common normal, physiologic cause of a high gastrin that doesn't mean anything. So it's very important to interpret gastrin in the presence of whether the patient has produced or is producing acid or not. So as a gastroenterologist, very often if I wanted to get a sense of why my patient would have a highish gastrin or if I was even contemplating getting a gastrin, I would do it at the time of endoscopy because they've fasted and they now have a scope in their stomach and you can suck some juice up at the same time as getting the gastrin. If you have a high gastrin and a high acid, by definition, you've got Z-E, and that's gastrinoma. If you have a high gastrin and a low acid, by definition, you can't make anything to interpret that because it could be from treatment, it could be from PA [pernicious anemia], it could be from a whole lot of other things. People tend not to do that frequently, but it was just one of mine sort of craziness, but it helped me manage my patients a lot better by having that knowledge.

Lisa Yen:

And we're so glad you have so much knowledge in this area. So we talked about a lot about Z-E, I know that it's something you know a lot about. You talked also about MEN1 and what conditions and complications it puts someone at risk for. For Z-E, what conditions or complications does the syndrome maybe put someone at risk for?

Dr Metz:

Well, first of all, there was a concern that a high gastrin level might be deleterious to your health in general. There was a time people were worried about high gastrins causing or being associated with pancreatic cancers or colon cancers because gastrin is a trophic hormone effect. In fact, when you endoscope patients who have Z-E, one of the features I didn't mention yet, is hypertrophic folds. So very thickened folds at the top of the stomach because they've got such big parietal cell masses that they get this big, thick folds in the stomach. And is that in itself a concern? It's really not a concern. So, gastrin itself and high gastrin levels themselves are not necessarily a problem. And in fact, we know that because people with pernicious anemia, as long as their B12 is replaced and their anemia is controlled, they have essentially a normal lifespan, other than having a slightly higher risk, which we've already discussed, for getting gastric cancer.

In fact, what you do see in all kinds of neuroendocrine tumors and maybe a little bit more with Zollinger-Ellison are secondary hormonal syndromes and I think that might be what you're alluding to. So, some patients who have widespread long standing metastatic Z-E can develop secondary tumors like an ACTH production, so the tumor starts making ACTH as well as gastrin. And then those patients can get Cushing's Syndrome. And they get very pigmented and they get diabetes, and they get striae and it's a very serious dangerous condition. Some patients get

secondary hormonal syndromes with parathyroid hormone producing tumors, a PTH-RP tumor which is like a parathyroid disease we mentioned with MEN1, but there the high calcium relates to a hormone produced by a widely metastatic neuroendocrine tumor. They often are associated with Z-E, and they often associated with MEN patients, but I don't think Z-E and gastrinoma is the “sine qua non.” So, in other words, you could potentially get secondary hormonal syndromes with other widely metastatic neuroendocrine tumors, not just Z-E. Z-E and gastrinoma, as I mentioned, tend to be more common, and that might be why the association occurs. I don't think I've actually seen patients with widespread carcinoid getting secondary syndromes now that you mentioned it, but I'm certain that it's potentially a possibility. And the reason I mentioned that one is because carcinoid syndrome is roughly twice as common as Z-E, and insulinoma. And insulinomas, just remember, differ from all the other neuroendocrine tumors in that day tend to be singular and often benign. 85% of insulinomas tend to be benign and are therefore cured surgically early on. Only about 15% of them, it seemed to be malignant and potentially develop metastases.

Lisa Yen:

Wow, thank you for that. So, I know many people have endoscopies and ulcers are common. So if you're someone who doesn't have a NET diagnosis, and all of a sudden I'm told I have an ulcer, does this mean I'm at risk for cancer? And what if I am a NET patient and I have NET in a different part of my body? What does this mean in terms of my NET?

Dr Metz:

That's tricky to sort of get a complete handle on but if a person comes to an upper endoscopy, and they find an ulcerated lesion, the most important thing is if it's in the stomach, I'm not talking about the duodenum. So duodenal ulcers are almost never malignant, but gastric ulcers are not always from peptic ulcer disease, which sounds weird, right? But a peptic ulcer is called a peptic ulcer because you develop the ulcer as a consequence of autodigestion by a hormone called pepsin. Pepsin is a proteolytic enzyme, and it needs to be activated and it's only activated when that pH in the stomach is less than four. So, if you have activated pepsin, you will get autodigestion and ulcers. But there is one type of ulcer in the stomach that doesn't matter if you have acid production or not, and that's a cancer.

So gastric cancers, which are primary lesions can outgrow their blood supply and develop ulceration and they look like an ulcer. And so, the dictum for gastroenterologist is if you find an ulcer and there is no acid, think of a cancer. So, ulcers could potentially be a gastric cancer and those are going to be people who are at risk. So, they usually are going to be a H. pylori infection. Anyone who has an ulcer and not a cancer, because you biopsy these things when you find him—any gastric ulcer needs a four quadrant biopsy by the gastroenterologist when they find him. But any ulcer that is not a malignant ulcer that is a true peptic ulcer, you need to think of the causes. The most common cause by far, H. pylori infection. If you find the HP, test. Test, diagnose, treat, prove cure with breath testing or some other method stool testing. And then you don't have to worry about it again. Of course, particularly common in Asian

populations in America, but everybody is at risk. And South Africa where I come from H. Pylori was ubiquitous. And I, I was studying H. Pylori at one time and they said to us, “Anybody in the room hasn't had a breath test?” And like an idiot, I put my hand up and I felt like a million dollars in those days and I got back to the office and there was a fax on the machine and said, “Guess what, you've got H. Pylori,” so I treated myself and that was that. But very common in asymptomatic individuals around the world.

The next one is non-steroidals. As we've discussed, if you have a nonsteroidal-associated ulcer, also stop the nonsteroidal, treat the ulcer to healing and don't start an NSAID again, unless you need it. If you need it, that's why you’re on prophylaxis, as we discussed earlier, with a PPI. So anyone under the previous history of an ulcer, whether you're under or over 70, whether you are or aren't on aspirin as well, anyone with a history of a peptic ulcer should be on a maintenance in that setting, unless the cause is removed. So those two account for almost all peptic ulcers, but we do talk about a non-HP, non-NSAID ulcer. If you have a non-HP, non-NSAID ulcer, in other words, if you have a real gastric or duodenal ulcer and you don't take NSAIDs. And you know, the patient has to be as honest as they can. They have to remember things like Alka Seltzer. Alka Seltzer has an aspirin in it, right? So makes sure you're not taking over the counter aspirin and even low dose aspirin is enough to cause ulcers. And so, most of the people who should be on prophylaxis are those that are cardiac patients on aspirin and with a little bit of arthritis. You know, any 75-year old aspirin-taking patient you should think about. In those sorts of settings, if you don't have an ulcer from an aspirin or an NSAID and you don't have H Pylori, that's when you think non-HP, non-NSAID ulcer, think Z-E. But remember another distinguishing point: gastric ulcers are not Z-E ulcers. Ulcers in the stomach usually come from underlying inflammatory conditions associated with a little bit of acid production. Ulcers in the duodenal them come from lots of acid production and less underlying inflammation. So, it's a hypersecretory type ulcer. And Z-E is usually a DU [duodenal ulcer], generally not a GU [gastric ulcer], although antral ulcers can be either, so the ulcers right down at the bottom of the stomach close to the duodenum.

Lisa Yen:

Wow, thank you for that very thorough primer on ulcers. So the last question I'll leave our audience with and ask for you is, “What are advances for gastric nets, gastrinomas or Z-E syndrome that we should be aware or excited about?” And “What last words of hope would you like to leave the NET community with?”

Dr Metz:

So, you know, I always have said to my patients that we’ll grow old together, rather than you having a terminal disease. I think, you know, in the last decade or two, that has been proven more and more real in that neuroendocrine tumors are chronic diseases, as opposed to deadly cancers in most patients, and especially with the lower grade, which is the more common diseases and even the G2 patients. The site of origin isn't really that much important. The productivity of any hormone syndromes isn't really all that important. It's stage and grade and

careful management. And in the last few decades, we've had a whole slew of new treatments come along. I mean, I was always a big fan of PRRT. And I think, you know, it has really shown to change the landscape in a dramatic way. I think there's potentially great future in new kinds of radiotherapies. The alpha therapies, maybe. Other beta therapies. I think from a genetic perspective, we may start learning about some kind of agents that are going to be able to be used in certain patients. I think that's another area that's growing. The imaging has improved so much that you can really get a much better handle on status and distribution of disease and therefore individualize therapy a lot more. I mean, while I have to admit and accept that certain patients can have very serious, aggressive, progressive disease, and it's really a tough thing to live with, but most patients should see the idea of getting a diagnosis as early as they can. Obviously, there's often a delay. But once diagnosed, get yourself to a physician who has some experience and knowledge so that you can have the best chance for a good cure early on and/or a good debulking very early on. I still have favor of good debulking surgeries and once you've reset the clock, SSAs are tremendous. And they are developing all sorts of new ways of administering these agents in time. And I think therapies beyond that, whether it's PRRT-related, whether it’s liver-directed therapies, which are really spectacular in selected patients appropriately. You know, the aim here is to give people good quality life for as long as possible. And optimism is something worthwhile. I've had patients over the years now that have done very well for decades.

Lisa Yen:

Thank you so much, Dr. Metz. What an excellent summary of the landscape of the treatments and what's on the horizon. Thank you so much for being a pioneer in this field, for pioneering what it is to be a neuroendocrinologist, for all your work, clinical work, the trials and everything you've done as a leader in this field to move this field forward, and to provide more treatments and better quality of life for those of us who are affected. So, we just want to thank you from the bottom of our hearts. And thank you for this time, and we're really grateful for all you do.

Dr. Metz:

Well, thank you for those words. I'm blushing.

Lisa Yen:

Well, thank you, and we look forward to seeing you again sometime soon.

Dr. Metz:

Great. Have a good day.

Lisa Yen:

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