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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.

One of the most important things to know about NETs, is that they are really not just one disease. While all NETs form from neuroendocrine cells, they can vary immensely from one tumor to the next- behaving very differently and requiring very different treatment. One of the factors that can completely change how a NET presents is where it starts in the body; what's known as its primary site. We're going to use the next episodes of NETWise to discuss three of the most common primary sites. We will cover

lung NETs, small bowel NETs, and P-NETs in detail and describe their unique features like you've never heard before. Stay tuned and subscribe to NETWise to catch all of these special episodes.

To begin with, we're going to talk about Lung NETs, also known as "thoracic" or "pulmonary" NETs. Lung NETs are often less frequently discussed and reported on than those that begin in places like the pancreas or GI tract, and awareness of them remains unfortunately low among the doctors who specialize in lung disease. This can make it frustrating for Lung NET patients to find good information. Here's Dr. Aman Chauhan, from the Markey Cancer Center at the University of Kentucky:

***Chauhan:** "I don't think there's a lot of educational material about thoracic NETs as compared to carcinoid syndrome or GEP-NETs. So, I think this would be very helpful for patients."*

As with all NET cancers, Lung NETs are often tricky to properly diagnose. They do frequently present with symptoms, but they are often symptoms that can be easily mistaken for other much more common conditions like asthma or chronic obstructive pulmonary disease (COPD). Here's Dr. Nathalie Lui, a thoracic surgeon at Stanford Cancer Center, followed by Dr. Robert Ramirez, from Ochsner Medical Center outside of New Orleans in Louisiana, and Dr. Andrew Kaufman of Mount Sinai Hospital in New York City:

Lui: "This is a really common presentation for patients with central tumors because they block the airway and it's much more common for patients to have asthma than a neuroendocrine tumor."

Ramirez: "Shortness of breath, cough, specifically... sometimes patients can come in coughing up blood, wheezing, just these chronic respiratory complaints. Sometimes pain can come along with this."

Kaufman: "Some people will have a recurrent pneumonia, and this may be a totally young, healthy person that keeps getting diagnosed with an upper respiratory infection, mainly because there's a propensity for these tumors to grow within the airway and block the airways, leading to pneumonias."

Ramirez: "And rarely, there's a hormonal component to it as well. So, similar to some of the GI neuroendocrine tumors."

But very often these tumors, especially the less aggressive ones, are discovered by accident, when a scan is done for some other reason.

Ramirez: "You know, I've seen this plenty of times- pre-op visit for a knee replacement and they get a chest X-Ray, and they say, 'Oh, you've got a lung mass there.' And the patient had no idea about it, and they've been asymptomatic from it."

However they're discovered, the first step is always additional scans and a biopsy so the tumor can be properly graded by a pathologist. This is because there is a wide range of different kinds of Lung NETs, which have very different characteristics.

Ramirez: *"They're on a continuum - from very indolent cancers - like the ones that you can observe - to the very aggressive type cancers, that if I see a patient in the office this afternoon, I'm putting them in the hospital tomorrow to start chemotherapy. So, you know, that's where our pathologists play a very important role in the diagnosis and telling us exactly what this is."*

And rather than the numbered grades we use to describe other kinds of NETs, lung NETs are divided into four different named categories.

Ramirez: *"typical carcinoids, atypical carcinoids, large cell neuroendocrine tumors, and small cell lung cancer."*

Kaufman: *"These tumors, while they're all sort of housed in the lung cancer group and housed in the neuroendocrine lung cancer group, they really have a wide spectrum of clinical behaviors and only share their microscopic characteristics and fundamental cell type of origin. They really just in reality behave very differently."*

These categories can be a little confusing to understand, so let's talk about them in more detail.

Think of the four types of lung NETs as four points on a line, with typical carcinoids all the way to the left, then atypical carcinoids to the left of center, then large cell NETs to the right of the center, and then finally small cell lung cancer all the way at the right end. Now picture a vertical line dividing our line in half - the two types on the left side, typical and atypical lung NETs, are classified as "carcinoids" because they are well-differentiated, and their cells grow and divide more slowly. The two on the right side, large cell and small cell lung cancers, are poorly differentiated and grow and divide more quickly. Our lefties, the typical and atypical lung NETs, are less aggressive, less likely to metastasize outside the lungs, and are often easier to treat. Moving to the right, large cell and small cell lung cancers are more aggressive, more likely to spread, and more difficult to treat.

Typical carcinoids often grow very slowly, sometimes developing for years without any appreciable symptoms. There are a number of treatment strategies that can be quite successful at controlling their growth, and the average 10-year survival rate for patients who have them is as high as 90%. Small-cell lung cancers, at the other end of the line, grow very quickly, there are fewer options for treatment, and the average five-year survival rate is only around 5%, making these one of the most aggressive and deadliest cancers.

Chauhan: *"So these are biologically very different diseases, and the way we manage them is very different."*

One commonality between all four types of lung NETs is their complexity. Lung NETs are best treated by a multidisciplinary team, with experts in oncology, surgery, pathology, endocrinology, and radiology all weighing in to help determine the best course of care. Let's look at some of the treatment strategies a care team might recommend for each of the four types of lung NETs.

In typical and atypical carcinoids, particularly those that haven't metastasized outside of the chest, the first and best treatment is often surgery.

Chauhan: *"If the patient's diagnosed in early stage, a curative surgical resection can get rid of the disease in most of the patients. So, there are patients who are cured."*

This is not possible in all lung NET patients, though, even those with typical carcinoid.

Liu: *"We generally operate for localized or locoregional disease that can be completely resected, and that means that the tumor is confined to the lung and the thoracic lymph nodes on the same side as the tumor."*

Before surgery, a series of scans and tests are required to make sure the extent of the disease is properly understood.

Ramirez: "I just had a patient the other day, it looked like this was an operable candidate with localized disease, but then when we got the gallium and it showed that that patient had a distant disease. So, then your treatment algorithm changes a bit."

Liu: "Patients obviously have to be good surgical candidates as well, so we check their functional status, we check pulmonary function tests to see how healthy their lungs are and make sure that patients won't be short of breath or require oxygen after we've removed a portion of their lung, we check their heart if appropriate, and we always recommend smoking cessation."

Chauhan: "Now, what type of surgery depends on the size of the lung NET, the location of the lung NET. The idea is to preserve as much lung as possible, and yet be able to take out all the tumor with negative margins. So, these decisions are made in a multidisciplinary tumor board—their thoracic surgeon is available, radiologist is there, medical oncologist, pathologist—all of us are here and we discuss what would be the best approach to treat this patient."

Depending on all of these factors, there are several different kinds of surgery that might be performed.

Liu: "Most commonly, we do a lobectomy. So, the lung has three lobes on the right and two lobes on the left, and generally we like to remove the lobe that the tumor is in,

so we take out all of the lung tissue around there, as well as all the lymph nodes that the tumor could drain into. If we remove one lobe, it's called a lobectomy; two lobes, a bi-lobectomy; if the tumor involves all of the lobes on one side, then we take out the entire lung on one side and that's called a pneumonectomy. It's also really important that we take out all the lymph nodes that are accessible on the side of the chest that we're operating on, and that's called a lymph node sampling or dissection."

In some cases, when the position of the tumor allows it, less invasive surgeries are sometimes possible.

Liu: *"So for patients who have tumors that are more central and involving the airway, sometimes we do lung sparing surgery. And so, we found that we can remove a piece of the airway alone and leave them with more of their lung. And so now we do what's called a sleeve resection for tumors in this area. And so, we'll cut on either side and remove this sleeve of airway. And then we have to sew the two sides back together. And there are certain lobes where that is easier or harder or even impossible, but it's really nice for patients with tumors in certain locations, because they can be left with more lung, which leads to a better quality of life."*

There's also a lung-sparing procedure available for peripheral NETs, called a "sub-lobar" or "wedge" resection, but its use is somewhat controversial among surgeons. While it is less harmful to the healthy lung surrounding the tumor, some worry that it

doesn't remove enough tissue to prevent the tumor from reoccurring.

Liu: "So surgeons have been really interested in whether we can remove just a sublobar resection for patients, and we have found that there may be a role for very small tumors that are at the edge of the lung that don't have any lymph node involvement, so really the peripheral tumors at the very earliest stages. However, there's still a lot of caveats about that, because we are still missing lymph nodes, so it's important to check those. We would only do it with the very well-differentiated tumors with the lowest grade, so if patients end up on the final pathology, if that result differs from the preoperative biopsy and patients have atypical carcinoid, then we would really recommend that they get the entire lobe removed, which could be another surgery. So, for me in almost all of my cases, I would still recommend a lobectomy and an anatomic resection, unless patients just are poor surgical candidates."

There's also some question about whether it's possible to treat lung NETs with a technique called "bronchoscopic" or "endobronchial resection", where tumors are removed by means of a long, flexible device called an endoscope, which is usually lowered into the lungs through the throat, a much less invasive option than any kind of chest surgery. Again, some also fear with this procedure that it's too difficult to make sure that all of the malignant tissue is removed.

Liu: "So again, endobronchial resection may have a role for the entirely intraluminal tumors that don't involve the wall of the airway, however, this requires a highly trained interventional pulmonologist or surgeon, and it's a little hard to really determine sometimes at the beginning whether a bronchoscopy is going to work. There's no lymph node assessment when they do the endobronchial resection, and it requires a lot of bronchoscopic surveillance, so not just the noninvasive CT scans, but in invasive procedure. So, for now, again, endobronchial treatment is mostly reserved for patients who are poor surgical candidates, although it can be useful for patients who have a pneumonia because the tumor's blocking their airway."

If one of these surgical treatments can be performed for your typical or atypical carcinoid, it's possible that no other treatment will be necessary.

"My name is Dave Bjork, and I live in Georgetown, Massachusetts, which is just north of Boston. I'm married and have three kids and I was diagnosed in 1998. I'm 58, so I was 37 years old at the time. Non-smoker, very active. My kids were very young at the time. They were five, three, and one years old, my three boys. It came as quite a shock to me.

I actually had pneumonia and put on antibiotics and, you know, kind of went on my way. And then about six months

later, I got sick again and went back in and, and once again I was diagnosed with pneumonia. And my doctor at the time, his response was, 'you know, you work a lot of hours, you have three young kids, you're exposed to a lot of stuff, yada, yada, you get run down.' And, you know, my wife, being a nurse, she was like, 'that doesn't make sense, because, you know, you shouldn't get pneumonia.'

But I was fortunate because this second time that I got pneumonia, the radiologist noticed that the infection was in the same spot, and so he sent a note suggesting to my primary care doctor that I get a CAT scan to further investigate. And that's when they found out that I had a tumor in my lung, and that was what was causing the infection, 'cause there was a blockage in my lobe.

When I got the phone call from my doctor...that's what I often talk about, often write about. I remember that night. I was out, it was a going away party for a friend who was leaving the job, and we met at a restaurant, and I got the phone call. And I remember it was cold. I remember it was freezing cold. And he said, you know, 'Dave, you have a tumor, you have cancer, and you need to come see me.' And those words were like, oh my God, it was just...that night was just, it was just awful. And that's what people talk about, that's that emotional part of when it all becomes a reality, it's just like, Holy moly. You know, you just got... 'I have cancer' and that's that you hear that C word and it changes your life forever, it really does. And being the age that I was, you know, with my kids being so small, that

I knew that they probably weren't even going to be old enough to really grasp what was happening, you know and the impact that was going to have on our family. It was terrible.

The surgery was a success, and in the surgery, they actually also take samples of your lymph nodes. And so, I knew, once I recovered ... it was in my room, the first time I saw my doctor, he told me that there was no spread of the cancer. They checked, it was clean margins and there was no spread into lymph nodes. So, I knew, there was a really good chance that they got it, they got all my cancer, and I wasn't going to have to have any further treatment.

The only thing I had to do was go back in six months for a bronchoscopy, which is a test under a full anesthesia again, where they go back in with a scope to look at things and make sure everything's okay. And there's no presence of cancer and whatnot. But there was no other treatment after that, and I've had a great outcome, so I live a life of gratitude ever since."

Even though surgery can be curative in typical and sometimes even in atypical NETs when they're caught early enough, it's important to remember that even the slowest-growing lung NETs are malignant, and you have to keep monitoring for a while after the surgery to be sure that they haven't returned or metastasized.

Ramirez: "The majority of times when, when these are picked up, these are picked up at an early stage. And in many cases, the patients will tell me that they were told that this is a benign tumor. 'Don't worry about it. It just needs to come out and you never have to think about it ever again.' And clearly, we know that that is incorrect and that this is indeed a cancer, a real cancer with the potential to metastasize both locally and also to distant sites.

And where I see patients fall through the cracks, is sometimes they'll go to the surgeon, they'll get their lung carcinoid removed and never have any follow-up anymore. And sometimes, you know, they come back six, seven, eight years later, and now they've got distant disease."

Sometimes surgery isn't an option for low-grade Lung NETs, because they've metastasized beyond the local lymph nodes.

Chauhan: "So advanced disease is a thoracic NET patient or thoracic typical carcinoid patient has already had metastatic disease at presentation. When we did the scan, let's suppose, there are liver mets or bone mets. Those patients are unfortunately not curative. You cannot cure them. The goal shifts from cure to palliation, to prolong

their life and control the tumor as long as possible. And we do have few options."

One of these options for extremely slow-moving disease, is simply observation. Some of these cancers can spread so slowly that the growth is barely detectable, and in those cases, treatment might not be necessary until the spread begins to cause symptoms. This is often referred to as watchful waiting or watchful learning.

When treatment does become necessary, the first line is often our old friends, somatostatin analogues, which as we've discussed in other episodes as a popular treatment with many kinds of NETs.

Chauhan: *"If the patient is symptomatic, clearly we need to start therapy and our upfront or frontline treatment of choice would be somatostatin analog. And both Octreotide and Lanreotide are used in common practice, which are long acting form of somatostatin analog once a month. And they work quite well".*

Somatostatin analogues can also be useful in the treatment of a very rare NET-related condition, known as DIPNECH.

Ramirez: *"It stands for 'Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia', it's a mouthful, so, which is why we call it 'DIPNECH'".*

DIPNECH is a condition that causes the development of many small benign growths in the neuroendocrine cells in the lungs, that are not themselves cancerous, but seem to create a tendency for NETs to develop down the line. DIPNECH can cause uncomfortable symptoms, though, which often resemble severe asthma, and recent research shows that these symptoms can be alleviated by taking somatostatin analogues.

Ramirez: *"What we have learned and what Aman and I described back in 2015 is a series of patients who had benefit with somatostatin analogues, and it's not so much that it, as far as we know, slows the progression of this, but helps out with the symptoms, primarily with cough."*

Something interesting is that both of these are what is known as "off-label" uses of Somatostatin Analogues, meaning that these medications have not been approved by the FDA for the treatment of either DIPNECH or typical lung carcinoids. Unfortunately, it's quite common with rare conditions that there just haven't been enough studies to secure official approval.

Ramirez: *"So just because somethings not FDA approved per se for a specific type of cancer, doesn't mean that we can't use it. So, for instance, somatostatin analogues, these are not FDA approved for neuroendocrine tumors in the lungs, you know, but there is lots of data to suggest benefit."*

There was a recent effort to gain FDA approval for the use of somatostatin analogues in lung NETs but unfortunately it was not

completed because not enough patients enrolled in the clinical trial.

Ramirez: *And this was a worldwide study, called the SPINET trial, they had accrued over a course of, I believe two to three years, but it was stopped I believe in 2018 because they were a long way away from their accrual goal. And that data has yet to come out in publication, so, you know, what they did accrue and how those patients have done, so, we have to rely on some of the retrospective data."*

Nevertheless, there's enough retrospective and anecdotal evidence to make somatostatin analogues a preferred treatment choice for lung NETs for many oncologists.

When tumors progress further, there are other options. One of these is the only drug currently FDA approved for lung NETs, the MTOR inhibitor Everolimus, which goes under the brand name Affinitor.

Ramirez: *"Most people tolerate this medicine pretty well, but I'd tell people this is not going to make their cancer go away. It's unlikely to make it shrink. But it's certainly, you know...the hope is that with this treatment that we will stop it from growing. And I have had patients on this treatment for a long duration, but at the same time, we always have to think about, all right, What else is next? What else do we have?"*

Chemotherapy options like the capecitabine/temozolomide, or “cap/tem” combination, may be a second- or third-line option, and many clinicians are very excited about the possibilities for nuclear medicine treatments such as PRRT.

Chauhan: *“Out of all those treatments, I think that one for the most promising one to try would be PRRT. As you’re all aware, PRRT has been FDA approved for use in progressive midgut or GEP NET patients in the US, however, the FDA indication did not include thoracic NETs. And that’s because thoracic NET patients were not included in the NETTER-1 phase three trial, which led to that the approval of Lutathera. However, we have a lot of data from Europe where PRRT has been in practice for 10, 15 years, and the data clearly shows there is activity in thoracic NETs, as long as patient’s neuroendocrine tumors are expressing somatostatin receptors. So, in our practice, we commonly employ PRRT, as long as insurance approves it, and as long as the patient has a positive gallium scan.”*

The next two kinds of lung NETs, atypical carcinoids and large-cell neuroendocrine tumors, are very rare and less well understood, and so their course of treatment is less well defined.

Atypical carcinoids are more aggressive than typical carcinoids, and they metastasize faster and more frequently, but there is a wide variety within that designation. Exactly how aggressive

they are is measured by something called the "mitotic index", which describes how quickly cancer cells multiply. Atypical carcinoids with a lower score on the mitotic index are treated in a very similar way as typical carcinoids-if they have not metastasized, surgery is an option, and if they have, familiar NET treatments like somatostatin analogues, MTOR inhibitors, and PRRT might be used.

Treatment for more fast-growing atypical carcinoids is more likely to involve options like radiation and chemotherapy.

Large cell NETs are also sometimes operable, though less often, and when it is done, it usually has to be followed immediately with other treatments to prevent the spread of the disease.

Chauhan: *"In this particular case, if the surgery is done and resection is done in large-cell neuroendocrine cancer, adjuvant treatment is recommended, either giving chemotherapy or radiation after the surgery, because the chance of micro-metastatic disease left behind is very high. These are very aggressive cancers, and even if they have gotten the tumor out, there is a chance that there could be microscopic disease."*

After surgery, or when surgery is not an option, these tumors tend to receive treatments such as radiation and chemotherapy, very similar to what we'll hear about for small-cell lung cancer. Interestingly, though, some current research is showing that a subset of large cell NETs, seem to have an internal

biology that more closely resembles forms of non-neuroendocrine lung cancer than other kinds of NETs.

Chauhan: *"you know, recently, there was this really interesting study from Memorial Sloane Kettering, and what they found, when you do next-gen sequencing on these large cell lung carcinoma patients, a subset of them—about 40% of them—show genetic signatures which are similar to small-cell lung cancer, and about 60% of them show genetic signatures of non-small-cell lung cancer, like an adenocarcinoma. So, we are now learning that this large cell neuroendocrine cancer could be molecularly very heterogenous.*

This is an area of active research, we're still learning more and more about it, but for practical purposes, most patients get treated just akin to small cell lung cancer, with platinum-based chemotherapy, but I'm not surprised a lot of doctors out in the community also employ non-small-cell lung cancer regimens to treat pulmonary large cell neuroendocrine cancer."

At the other end of our spectrum, we have small cell lung cancer, which is extremely aggressive and extremely difficult to treat.

Chauhan: *"So if it's a limited stage small cell lung cancer, that being it's still in the lung or thoracic*

cavity, it's still not spread. Even within the thoracic cavity, it's not in multiple spots, just one area and can be covered by one field of radiation-and these patients are treated with combination of chemotherapy-and the choice of chemotherapy is a platinum doublet, can be cisplatin etoposide or carboplatin etoposide- followed with concurrent radiation. So, the patient also gets radiation, external beam radiation to the chest while getting the chemotherapy. That is the standard treatment."

Even if this treatment works well, it only brings five-year survival from 5% up to 10% of total patients.

Chauhan: *"On the grim end of the spectrum, the patient has extensive stage small cell lung cancer at time of diagnosis, which unfortunately most of the patients do, because this is a cancer, which is very aggressive. Sometimes the duplication rate or doubling time is almost as high as 14 days, so the tumor can actually double in size in two weeks. This is how aggressive this cancer is. So, it's not uncommon for us to see the patients with extensive metastases at time of diagnosis, and these patients can have mets in brain at time of presentation, adrenal glands, liver, bone, lymph nodes..., So, the treatment for extensive small cell lung cancer is palliative chemotherapy. We start off with platinum- based chemotherapy, carboplatin etoposide, or cisplatin etoposide.*

And most recently the big advancement which has been made in this field is addition of immunotherapy. So, immunotherapy now is a standard of care, FDA approved, and we often used Ateziluzimab, which was the first FDA approved immunotherapy agent in the frontline setting for small cell lung cancer.

Now, despite our aggressive chemotherapy and immunotherapy, unfortunately most of the patients would eventually progress as we go further down the therapy. Third line, fourth line, the response rates in small cell lung cancer unfortunately dips to 10%,15%. So, chemotherapies often don't work, cancers become much more resistant, and patients of course have a rapid decline in performance status, cannot tolerate more chemotherapy. So overall survival in metastatic small cell lung cancers, unfortunately one to one and a half years, even today.

So, this is an area of unmet need and it's called a 'recalcitrant cancer' because we haven't really made a major advancement in small cell lung cancer in the last 30 years."

Something that all four kinds of lung NETs share is a tendency to metastasize into places that are less common for many other kinds of NETs. While they can spread to the liver the way small bowel and pancreatic NETs tend to do, they also can often metastasize to the bones.

Ramirez: "So, bone metastasis can happen anywhere. Frequently I see them in the spine, I see them in the ribs, we see them in the skull bones, and the long bones as well. So really, really anywhere. They can present with pain or they can present with fracture and sometimes these things are just seen on imaging and they can be asymptomatic.

You know, the thing we get concerned about the most is when these cancers metastasize to the spine, because at that point, these things can impinge on the spinal cord. If this pushes too far, this can lead to paralysis. So that becomes one of the few oncologic emergencies, with that being spinal cord compression.

So, when they cause pain, if it's a localized area of pain, sometimes we can use a short course of targeted radiation to help alleviate that pain. There's some groups that can sometimes go in with their interventional radiologists and ablate that site, but it's more common to use radiation for that. The other agents that we use to help treat bone metastasis are those that help prevent that bond from breaking. So, there's a couple of different medicines, dielectronic acid, and also a medicine called Denosumab, which are both useful to try to help prevent these types of events."

The aggressive small cell and large cell neuroendocrine lung tumors can also metastasize to the brain.

Ramirez: "With the higher- grade cancers, we look for this. We know that there's a high risk of this disease going to the brain, so right after the initial diagnosis, we always get an MRI of the brain to look for this. In the lower grade tumors, it's uncommon, so we don't look for it unless there are symptoms. So, symptoms, including headache, visual changes, if there's any focal weakness, certainly if there's been a seizure...I had a patient just about a month ago who developed symptoms of having a stroke. And we sent her for an MRI and I was expecting her to have a stroke, just based on the symptoms, but it turned out it was a brain metastasis. So, when someone has a brain metastasis, in many cases, the initial problem is swelling of the area around that particular brain met. You know, it's an irritant to that tissue. So, we initially start some steroids to help bring that swelling down. If the patient has had a seizure associated with this, we'll put them on antiseizure medication.

Now the treatment of it really depends on where it is and how big it is and if there is more than one. If there's one or sometimes more than one that are in desirable locations, where they can be taken out, we send these patients to the neurosurgeon and who takes them out. The other option for treatment with this is targeted radiation, where we can actually give this patient very focused radiation that kills off that spot in the brain."

Because lung NETs are a small subset of what is already a relatively uncommon cancer, the other thing all four kinds have in common is that there is still a lot to learn about them and how they behave. But research is being done, and it's only through the participation of motivated lung NET patients that it continues, and our understanding of these NETs continues to grow. So please, if you or someone you know, is currently living with a lung NET, find a doctor who specializes in lung NETs, seek out research studies and clinical trials that are enrolling patients like you, and be a vocal part of the larger NET community. Together, we will continue to improve our understanding of lung NETs and support the development of improved treatments.

Join us for the next two episodes of NETwise, when we'll continue our exploration of primary sites with two of the most common-NETs: P-NETs and small bowel NETs.

Thanks for listening to NET Wise. 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.

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