Peptides and Amines: What Are They and What Do They Do?

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He's another trailblazer. So, please help me in welcoming Dr. Thomas M. O'Dorisio.

It is such an honor to be here. I very much appreciate the invitation. I appreciate Dr. Woltering's efforts, the efforts of the steering committee and the effort of the entire CalCF group in coming up with this unique conference. I am an endocrinologist. That is almost an apology, while at the same time it's giving witness. I've taken care of diabetes for a long time and I've taken care of folks with neuroendocrine tumors. I, myself, have diabetes. So, I want to just share with you (and to all of you with whom I have a personal working knowledge and relationship with) that I greatly admire and respect you for your ability to take charge of your illness, because that is not an easy thing to do. And being on both sides of the coin, I can share it with you. When I had my heart problem, I went into the hospital and the only normal test I had was a prostate specific antigen (PSA). I was celebrating -- at least I had one normal value on my tests! Everything else was pretty abnormal, but I was ready to consume the family, get a little bit of personal attention, and all of them, to the person (starting with my wife Sue), said, "Now you know, we're not your caregivers --- we're your coaches. Now, as coaches, we want you to do this, this and this." And that's the way it's been going ever since.

But, what I'd like to do to today in the time we have together is to pick up on the things that have been said by the master, Dr. Warner. I always learn so much when I listen to him - and often repeat a few things. I would like to start to bring us to the reason and the rationale for why everything's working. I mean, Sandostatin is no accident, as you probably know better than I, but it came along with a definite drug development rationale. It was a very definite endocrinologic discovery based on its native counterpart somatostatin-14. We learn so much, at the same time, because of Sandostatin, or octreotide acetate, is presently the only game in town, and will be for a few more years. Over the years, we've learned a little bit more about what happens to hormones when they get to the cell. We know all about estrogen, we know all about testosterone, and we know about thyroid hormones. Those have different mechanisms than the hormones that Dr. Warner was alluding to, including serotonin, chromogranin A or pancreastatin. We know that there is a very sophisticated system of hormones in our body. When they work too much or functional tumors make too much of a good thing, we have problems. When gastrin was discovered, it was discovered because of the holes that it would put into stomachs, via gastric ulcers. When vasoactive intestinal peptide (VIP) was discovered, they had to work backwards because people would present with profound diarrhea. Dr. Kvols talks about a patient that he cared for when he was at the Mayo Clinic who had diarrhea that filled containers that held gallons of fluid. This patient had a life-threatening condition. It was through patients like these that we learned about VIP. So, nature has given us lessons in peptide or hormone excess; thus, we know how hormones work normally in our bodies. And carcinoid tumors have been no exception to that rule. We'll allude to some of the remarkable hormones that carcinoids can make. But the point is that carcinoids are very sophisticated tumors. I consider carcinoids to be the diabetes of cancers --- because it's chronic and there's enormous hope for patients with this disease because there's a rationale for why there's hope. That's what I want to

share with you the next few minutes. So, there will be a little bit of the old Latin phrase "repetitio est mater studiorum", repetition is the mother of learning. Even before this talk, I expect that many of you are at the cutting edge about this disease and to have questions that I'm not going to be able to answer. I know many of you and I know the kind of homework that you do. It's a little like Irma La Douce with Jack Lemmon and Shirley MacLaine when Jack Lemmon is talking to Irma (Shirley) and says, "Well, I was in the war and there was an explosion", then he pauses and then he says to Irma, "Please be gentle with me". So, that's what I'm asking of you - please be gentle with me.

Now, this is my favorite slide - this is the evolution of neuroendocrine medical therapy. Dr. Gene Woltering and I worked on this slide and we'll hear a little bit of some of the more recent exciting developments in this disease when he gives his talk. But you can see that this has been a continuum, a progression of discovery in the GI system and in the neuroendocrine system. The hormones that we're talking about here are not the estrogens and the testosterones - those are called steroid hormones. I'm going to try to weave that concept (steroid hormones and peptide/amine hormones) back and forth. These are very simple cells [slide] that are neuroendocrine derived. That is, there is a nervous system and a release of peptides into the blood system by the endocrine part of the "neuroendocrine system". That's why they are called "neuro" and "endocrine", because they impact the nervous system and they also impact your body's other tissue. An endocrine substance is a substance that goes to another area of the body and affects that part by an "endocrine" action. That's called a hormone. It doesn't do its thing (necessarily) in the tissue right next to where it is made; it does it to another hormone or a distant tissue. And the controller of that peptide system - it is not the pituitary controlling the estrogen; it is not the pituitary controlling the testosterone, or glucocorticoids or thyroid. Rather, the neuroendocrine system that we will talk about today is a system that is controlled by a circulating peptide called somatostatin. Doesn't it sound like Sandostatin? As you can see, one of the most important things in that progression slide that I showed you before is the area was where you saw radiopeptide receptors. The discovery goes back to 1967; therein began the endocrinologic concept that a substance made in one part of our body can go to a cell somewhere else and that cell is it's target. The peptide can bind to it and exert an action. That's precisely what somatostatin/octreotide - Sandostatin - does. It has a specific inhibitory, down-regulation, turn-off-the-growth type of action.

You know about OctreoScan; Dr. Warner alluded to it. I'll show you another picture. There is octreotide; Sandostatin was first brought into the clinical arena in 1980. It was brought into widespread clinical practice in the United States on January 15th, 1989. It was FDA approved on that day for clinical use in the US. And there on the evolution slide is the RPR, which is the radiopeptide receptor-guided surgery technique that we've helped work out. Eventually it will hopefully be another arm of therapy for people to be able to have a very exquisite, tedious type of "berry picking" surgery in addition to the convention surgery, where we can identify small, 3 mm tumors and take them out because we're keen on them with a Geiger counter. That is proof of concept for it. Then we, of course, now have OctreoTher, (the yttrium-90 labeled somatostatin analog), and Lutate (the lutetium-177 labeled somatostatin analog), and we'll hear more about this as the day goes on.

There is a cell [slide]; that's the neuroendocrine cell. If you know some nervous system anatomy that almost looks like an axon body where all you're expecting to see at the end of that tip is a few dendrites. That's the kind of cell that we're dealing with. And it's got a clear area around the nucleus, and that's why the great Friedrich Ferter from Austria, classic anatomist, said something in pure German like "this is a clear cell", something like that. It was a shock when he saw these things. But anyway, it's a clear area. Now, these are totipotential cells, that is, they can make any of a number of things. The more de-differentiated, the more "unlike normal" they become, they start to become more primitive and they don't just get ugly looking, they can make other hormones. They then come back to basics. The more differentiated that cell is, the more control there is from somatostatin/Sandostatin. That's the key concept. That's the hope for everything. And where is the next step? It's obviously going to be putting those receptors, putting those keys into the locks into the cells, and then treating them with radionucleotides like yttrium-90 or lutetium 177 attached to Sandostatin or a look-alike that will attach to a new receptor. And that's where Dr. Sue O'Dorisio and several investigators in the world are going to be able to teach those tumors how to make receptors so we can treat them.

These are the tumors; you've heard already about them [slide]. Here is a schema - we're into the

cartoon of the tumor itself, and these are the tumors. You see a carcinoid; 55-60% of all adult neuroendocrine tumors in the United States are carcinoids. You heard an exquisite lecture from Dr. Warner delineating, from his gastroenterologist's point of view, the carcinoid. No better person can talk to the clinical observations in these tumors than Dr. Warner. Then there are the others type of neuroendocrine tumors, the neuroendocrine tumors of the pancreas, sometimes called islet cells tumors. Some of you may have carcinoid of the pancreas or stomach or lung. But there are also neuroendocrine tumors that aren't carcinoid by definition, as Dr. Warner showed you. Your tumor may be making too much gastrin, and that's called a gastrinoma; too much VIP, and that's called a VIPoma; or too much glucagon, and that's called a glucagonoma. Should carcinoid be called carcinoid tumoroma? No. Maybe it should be called a serotonoma. Or maybe carcinoids should be called substance P-omas because carcinoids can also make too much substance P.

In children, it's just the opposite. The point in the lower right corner of the slide is neuroblastoma, and its counterpart in the brain in children, is medulloblastoma. Whereas carcinoids have a 60% survival over 5 years, disease-specific, as we will see in adults, there is a 60% mortality rate in children across the board with neuroblastoma or medulloblastoma.

Now, this is the other concept. Recall now, these are cartoons and they're not embellished very much with hardcore data, but they serve to convey a message. The slide on the left is the neuroendocrine cell/tumor. What you see is the structure or somatostatin or its look-alike, Sandostatin, and on its right is a target cell. It can be the gastric cell that makes acid; it can be the secretory cell of the bowel that causes secretion and water loss. The point is, these cells all possess receptors for somatostatin, and that was the greatest shocking news. Because, when Sandoz (now Novartis) first made the compound, when Janos Pless and his team of 50 other people in Basel, Switzerland, made the look-alike of somatostatin in 1973, they did not know that there was more than one somatostatin receptor, one "lock" on a tumor. We now know, because of Sandostatin, that there are five locks, or five receptors subtypes, for somatostatin. And it happens that these tumors almost across the board possess (from 85 to 95% of these tumors) receptor subtype 2. Now that's great news, isn't it, for all of us in the room? When I went to Sandoz on a very cold January day, and they were introducing to us and showing us that their peptide Sandostatin actually saw receptor 2 but didn't see receptor subtypes 1, 3, 4 and 5 very well, I said simply (and that was the first and last time I was invited to Novartis home base), "Even a blind squirrel will find an acorn". I was hoping that I would get more of these compounds to work with in the lab, but that didn't work.

Now you can see how somatostatin binds to the somatostatin receptor. There is one specific piece of the somatostatin or Sandostatin that is responsible for binding. Here is a blown up picture. On the top is what God gave us, a 14 amino acid peptide; that means 14 little proteins stuck together just like you see it, in a ringed fashion. Obviously it would be in 3-dimensional in real life. And below it is what the "gnomes in Basel" did to the molecule that God made. You can see the similarity just by looking at the moieties. One of the little moieties that have been retained on both of the rings is an amino acid called lysine. Lysine is an amino acid that many and most of you are familiar with. It's lysine that docks into the somatostatin receptor. Once it docks into that receptor, this peptide then can exert its action on the analog, the look-alike, the analog, can then exert its action on that cell. And that action, by and large, for somatostatin (the grand controller of all of these peptides) is not to affect a steroid-based hormone like estrogen or testosterone, not ones like thyroid hormone, but to affect a peptide hormone like gastrin, insulin, or glucagon. The one single action is to regulate those cells so they don't go out of control. Now that, in part, explains why there is good data now arising to show that this is why these tumors are good news/bad news. It's because neuroendocrine tumors and their growth have been held in check and slowly growing while you don't know it. Because somatostatin in your body has continued to impact on the growth and differentiation on these cells "gone bad" which are now tumors.

And there's octreotide [slide]. Why do we want a peptide like octreotide? The people at Sandoz made a powerful drug with only 8 amino acids. Why is this drug so important? Because it lasts longer in the body than the "native" somatostatin molecule. Somatostatin in your bloodstream lasts less than a minute-and-a-half. Octreotide, given subcutaneously like many of you take it, lasts 90-120 minutes. Given in LAR form, the octreotide has the same half-life, but it's releasing slowly from small beads or polymer pellets over a month or so. Thus, the drug release happens as the polymers dissolve. It's still octreotide acetate but in a sustained-release formulation. And shown here is slightly modified

octreotide that really is the backbone of OctreoTher. In the OctreoTher molecule they replaced phenylalanine, there in position three, with a tyrosine. But you can again appreciate how similar that structure is to octreotide or even to the native somatostatin molecule. Another somatostatin analog that is in clinical use in Europe is lanreotide. And they try to say, "we are no worse than Sandostatin", and that's of basis of their efforts to come into the United States (equivalency), and that's what will happen. There will probably be a knockoff of octreotide that will come into the US eventually. Hopefully, this will happen because the somatostatin analogs are so expensive as we all know and appreciate.

It was really Dr. Kvols who pioneered getting octreotide into the United States with his carcinoid work at the Mayo Clinic. This is the only drug ever approved in the US using only data from "compassionate need" use of the drug; and yet, they did it. The Federal Drug Administration took Sandostatin and approved it in the United States based on 177 people with neuroendocrine tumors and 90 doctors beating all over them to make sure that their patients got enough drugs. As Dr. Kvols often says, Sandoz (Novartis) gave him 10,000 ampules/month to keep his patients healthy before it was approved.

This is a little bit of repeated information, and we're going to move through this quickly because you've heard it before. It's about the nature of neuroendocrine tumors. Remember that the phrase "neuroendocrine tumors" refers to a big bowl of fruit. It's a family of fruit, and within that family are carcinoids, in there are insulin-secreting tumors, in there are probably medulloblastomas, and probably neuroblastomas. So, different types of fruit, but they all fall within the basket of neuroendocrine tumors. They're derived, as I said to you earlier, from neural crest origin. They arise primarily, as we heard from Dr. Warner, from the gut. In adults, 60% of the all neuroendocrine tumors are carcinoid; 72% arise in the midgut and hindgut, and 22 or 23% of those, 60% are then in the pancreas, the foregut, part of the pancreas, stomach, or lung. You can see they're episodically secreting. Why do they episodically secrete? Why do people with growth hormone excess not always look huge and big all their lives? The answer to that question is that the secretion of growth hormone is under the control of the somatostatin molecule as part of a complex set of counter-regulation mechanisms. What's controlling it? Most probably somatostatin, because somatostatin binds to the growth hormone secreting cell and blocks the synthesis and release of growth hormone. That's why the symptoms are not often present and sustained when you have it early on, as Dr. Warner pointed out. They're episodic because somatostatin controls the secretion, and the secretion becomes normal. It controls serotonin release; it controls substance P release; it controls gastrin release so you don't burn your stomach out with too much acid all the time. Then when they become tumors, these neuroendocrine cells grow slowly and overwhelm the somatostatin, your protective system.

We heard that they preferentially go to the liver. Why is that? It is very difficult to show. Dr. Kvols can speak to it better than I can. But, when you think about the anatomy of our bodies, we have veins that take blood and waste to the liver so the liver can filter it and clean it. It happens that the tumors in the intestine are drained into the liver by a vein that is called the portal vein. It happens that the veins in the pancreas drain the pancreas' waste and bring it to the liver as part of the portal vein. That's why the "sponge" or filter for the neuroendocrine tumors below the diaphragm is the liver. That's the ultimate vein; it's the liver that gets consumed with the tumors siege. That's the thing we fight to keep back and hold back. We're going to hear about phenomenal ways to do it. Many of you might have had hepatic arterial chemoembolization. There are spheres now, yttrium-90 spheres. There are many different methods like radiofrequency ablation that can be used as therapy in these tumors. We're going to hear about those. Dr. Pommier, I am sure, will discuss many of these treatments. There it is on the bottom [slide], nothing new. It's all repeated. I see you lip syncing me as I speak. Somatostatin receptor subtype 2. It's all right there, under the regulation area of the slide. That's how simple it is. The cardiologists always say, "How many endocrinologists does it take to give a shot of insulin?" and then all the cardiologists laugh. This is one of those same situations: how many of us do you need to learn about this? There are many ways to explain it; sometimes you make it sound more difficult than it is, and I can't even do that.

Here [slide], we're just saying the same thing again, and what Dr. Warner said, 50-60% are carcinoid. Another 20% he brought that up beautifully because he pointed out the multiple endocrine neoplasia syndromes, both the type 1 and the type 2, these are familial, autosomal dominant genes with variable penetrance. So, there are familial patterns, and even familial carcinoids. I think Dr. Warner

has probably the 3 or 4 familial carcinoid patients in the US.

Carcinoid tumors were originally described in 1888. It's the oldest known neuroendocrine tumor of the body. It is published in Virchow's Archives, and it's name was coined from the German word "carzinoid" meaning cancer-like. In some respects, it's doing a disservice and an injustice to say the word carcinoid. We've heard about the new nomenclature for these tumors which is much more accurate: neuroendocrine carcinoma type 1, or grade 1, 2 and 3, maintaining the classic European classification of Capella and Solcia who talk about the typical and atypical carcinoid tumor. So, they're bringing the two together. Wick is the American pathologist. Capella and Solcia are the Europeans, and Dr. Oberg can correct me because he probably knows much better than I, but I believe they are the ones who really began the classification of neuroendocrine tumors after Friedrich Ferter in Europe described the neuroendocrine cell, the heilenzeilen, the clear cell that I showed you earlier.

This slide shows the incidence, 4,000 to maybe 8,000 new cases of carcinoid per year, depending on what you read. But what is different than new cases? Yes, that comes under rare cancer indication, but those are new cases. It's been estimated by one of the folks who visits us in the clinic that there are probably 68,000 known carcinoid cases and another 120 or 130,000 who don't know they have it. So, the prevalence is much higher. We've estimated for at least 2 or 3 years that the prevalence of this cancer, neuroendocrine tumors, is closer to 200,000 in adults. And why is that? It is because somatostatin keeps them regulated and under control until they break through and grow, or until they lose their receptors. This is one of the things that we hope doesn't happen.

This is the part of the slide that introduces the topic of hormones and what they do. We saw neuron-specific enolase (NSE). It establishes the essence of the neuroendocrine cell; it's that staining, that's a peptide in all of us. Chromogranin A we've heard about. It's a huge peptide that probably does have some biologic activity. It does turn on glucagon, and it has a fragment called pancreastatin. It's been shown in the biochemical literature that it turns on glucagon. What happens when you turn on glucagon? You antagonize insulin and you see diabetes; (i.e.) you can get glucose intolerance. No surprise that many folks may also have glucose intolerance with their carcinoid. And serotonin is a very important hormone. The four E's always turn it on: exercise, excitement, emotion and ethanol. That turns on, and that squeezes these larger cells, and these grape-like cells then squeeze out the serotonin. You can't break it down fast enough. The half-life of serotonin in people, the plasma existence of it, is less than a minute. Most people have a surge when they appear embarrassed and it goes away. People that are releasing more of it can't break it down, and then you have a pathologic situation where serotonin in high levels is starting to impact on your target tissue, such as your skin, to cause flushing or pellagra in its extreme form. Or excess Serotonin can cause secretory diarrhea, where you lose salt. Where goes salt goes water. Secretory diarrhea can be, as Dr. Warner showed, very, very bad. But also in there is corticotropin-releasing hormone, growth hormone releasing hormone. The bottom line is that these are hormones that exist in us normally. We didn't even know that for years. We didn't even suspected these peptides and counter regulators of peptides were there until carcinoid patients came along and taught us what they really do - by making too much of these. That's why these tumors are so sophisticated, so enigmatic, because there are probably 3 or 4 more hormones that we don't even know about in our bodies that are doing things now as we speak. These peptides exist undiscovered, and carcinoids and the carcinoid syndrome might give us those answers.

Again, the most sensitive test and the best marker, as we heard from Dr. Warner, is the serotonin. In general, I say as a rule that unless you have metastasis to the liver, you almost never see an elevated urinary 5-HIAA level; 5 HIAA is the biological, biochemical breakdown product of serotonin. That's been a hardcore fact in the pathology literature for many, many years. Pancreastatin is one marker I happen to like a lot; it is a split fragment of chromogranin A. It is more sensitive, I believe, and it is a very good marker for liver tumor changes. If it bumps up, it helps me personally, in my practice, to get a little more concerned about what's going on. Usually it precedes CT changes in tumor size by 2-3 months.

Carcinoid syndrome, as we heard, is not a disease; it's a syndrome, it's a constellation of symptoms. It's like Cushing's syndrome, which is caused by too much adrenocorticotrophic hormone (ACTH). The syndrome doesn't tell you where the primary disease is, though we know there's too much ACTH

and there is actually too much cortisol, a hormone that is not like what we have secreted from carcinoids (serotonin). Now, we saw this again from Dr. Warner, the cardiac fibrosis. Hopefully the incidence of this heart valve damage is changing. No one is able to stand on that big, long, tall tower and see the natural course that carcinoid research will take, but we are getting data that relates back to the classic work of Godwin from the National Cancer Institute. Vinick initially derived his figures from this work and Modlin has taken over this database and updated these reports from 1957 through 1997. A colleague at the University of Iowa has now looked at this database more recently. The point that I am trying to make is, as new therapies are designed, I hope we don't see those complications (of chronic battering of serotonin and substance P - mainly serotonin - on the heart valves) as often as we used to. I hope we're seeing less of it. In my own experience over the last 6 or 7 years, I have seen less of this complication. I honestly and firmly believe that I think is really due to the impact of octreotide acetate since 1989 in the United States. This is the work; these are 3 slides from Dr. Irv Modlin and his colleagues published in Cancer in 1997 covering 8,305 cases of carcinoid. Those were the cases that were started by Godwin in 1950. Then Godwin carried it through and presented his series in 1971. Irv Modlin then used their database for his 1997 report. This is close to the natural course of this disease like Dr. Warner was alluding to. Dr. Vinick showed on his graphs a very similar curve for the natural course of untreated carcinoid. That's the part you have to remember; it's untreated carcinoid, not carcinoid that has been treated intervened and interfered with. So, 5,468 cases were identified and lumped together with the others, and it became a huge tome, and I believe overall extremely well done. What we see are the numbers that Dr. Warner and I have been giving you, and that is the incidence of foregut tumors, which are comprised of lung, stomach and pancreas, and are, as you can see, about 25-26%. Midgut and hindgut make up the vast majority of the carcinoid tumors that make up 55% of all the neuroendocrine tumors in the adult.

This is interesting, and Dr. Warner has alluded to this, the PPIs, the proton pump inhibitors, and how they irreversibly raise gastrin. When you do that, you have a small, albeit real risk of inducing gastric carcinoids though most of these gastric carcinoids induced by PPI usage behave in a benign manner. People are using PPI drugs more and more in place of Zantac and Pepcid. But you can see what's happening. There seems to be an increased incidence of the bad ones, the ileal carcinoids and the gastric carcinoids. There seem to be trophic factors in our bodies that might be helping to raise this. Is gastrin one of those trophic factors? It runs hot and cold, and it's going to take years to see the impact of the proton pump inhibitors, like Prevacid or Prilosec or Nexium. But gastrin does cause growth.

There is the slide again from Vinick and Molinari. They were very, very clever. They took Godwin's theories up to about 1971 or a little later, and then did this curve. Remember, this graph is the natural course of carcinoid tumors that Dr. Warner showed to you. Just imagine everything that's being done to these tumors today: surgery, octreotide use, radiofrequency ablation, hepatic arterial chemoembolization, internal radioablative therapy. All of these therapies alter that curve and drive it back toward a normal survival curve. Why can you control carcinoid tumor growth with Sandostatin? You can inhibit tumor growth because the tumors cells have the sst 2 receptors. They are not autonomous tumors; they can be made to be under control, albeit there is a small percent that do not have the receptors or may lose them. I am also convinced from several patients' tumors (including tumors from 2 or 3 patients who are in this audience today) that I have taught the tumors how to make receptors. We did it with chronic use of octreotide. I have data that, in my heart, tells me that taking Sandostatin also helps "teach" the receptors how to make themselves on the tumors.

This [slide] is a schema that we use. It could be generically used and is used by all my colleagues, I am sure. What this needs is a facilitator like I hope to be, and people like you who are very articulate, well-informed people. But these people also need physicians who help make the proper decisions on what is the "correct" next step in the therapy of this disease. This slide talks about surgery on the left side; it talks about hepatic artery chemoembolization and embolization with yttrium-90 spheres on the right. It talks (up at the top) about somatostatin use - win lose or draw. Remember, somatostatin doubles your pleasure. It doesn't just inhibit the tumor's growth. It antagonizes what that tumor is making and it's effect on your target cell, wherever they are. It blocks serotonin's action on the target cells of the skin and the secretory cells of the bowel. So, you take octreotide for symptomatic relief. If your symptoms are being well controlled, you are probably controlling your tumor growth as well. Again, how do I know that you have receptors on your tumor?

Because, as Dr. Warner showed you, the OctreoScan told us that the tumor has these receptors by it's uptake in the tumor. What's the OctreoScan? It's octreotide; it's Sandostatin, except it's got a "Kodak picture maker" on the end of it. The thing that "makes" an image on the detector is called 111Indium. And that picture tells you you've got receptors.

There's a PET scan [slide], and yes, we do believe in positron emission tomography because I think it's a "reverse negative" of the OctreoScan. We have some information we've submitted for publication on this topic. Dr. Menda presented our work a couple of months ago at the nuclear medicine meeting, which really helps. I think in the foregut tumors, and I'd love to hear the comments of my colleagues on this, that it's been particularly helpful because I don't trust those as much as I trust ileals in knowing how they're going to go. If there's any increased activity of the tumor, the PET may be the first to tell you that. So, I use the PET, and as you can see it's part of the algorhythm as you get down toward treatment with internal ablative OctreoTher or Lutate and/or more conventional, aggressive chemotherapy, which we'll probably hear a little bit about from Dr. Kvols.

Here is a PET scan. This patient happens to be a multiple endocrine neoplasia person from West Virginia. She came in with a headache, she had kidney stones, and she had terrible ulcer problems for years. That's a classic Multiple Endocrine Neoplasia 1 complex of symptoms. I did an OctreoScan and lo and behold, she had 2 tumors that lit up because she had receptors on her tumor. No one could miss this big tumor because it was 2 cm in size, but the little one that was there (that we told the surgeon to be watching for) was only 0.4 cm in diameter. That was possible even without surgery. We knew there was a tumor in there that was just 4 mm in diameter. That's how accurate and how sensitive the principle of peptide hormones binding to their cell receptors and exerting an action in a normal physiologic way, and now in an abnormal way in a tumor.

Just to show you, we're very pleased with the box in the lower left corner. Dr. Sue O'Dorisio and I have worked for about 3 or 4 years to make an antibody specific to the receptor so I can actually see it. So, we made a receptor and antibody. You put a piece of that receptor subtype 2 into a rabbit. You threaten the rabbit with becoming rabbit stew, and they make an antibody for you. They used to use 15 and 20 rabbits, believe it or not, to make a single highly specific antibody. But we did a little sophisticated thing here and there and we had beautiful antibody, and were finally able with the help of specialty giants, immunohistochemical pathologists, in our case, Dr. Barry DeYoung and Dr. Frank Mitros at the University of Iowa. Shown on the right side with those little dark brown spots are actually the receptors for sst 2 in a carcinoid tumor that is replete with receptors. Not only that, but Dr. de Young now has used the classification of WIC neuroendocrine type grade 1, 2 and 3 and he thinks that we can almost predict which ones need to be attended to most forcefully when they're first diagnosed. That's something we don't have. Everything is well-differentiated, low-grade malignancy, and they crop up later. We don't understand it, but we're starting to be able to cone down. One of the things that this may help us do is to find out how many receptors were on that tumor at the beginning, because it's those receptors that we're going to exploit.

I'd like to say just a word or two about Sandostatin's effects on the target tissue. This is why octreotide was approved by the FDA - for a very narrow set of indications. Those included the control the secretory diarrhea of carcinoid and the flushing of carcinoid. You can see that Sandostatin really does block the flushing. It really does protect patients from getting into trouble. The diarrhea is improved in almost 100% of people if they take the right dose. This is why the "clinical cart got ahead of the research horse" so quickly. It was barely studied, research-wise in the pre-clinical arena, before it came into clinical use the United States. It was approved for use so quickly because of its dramatic effect on the quality of life.

This is what the LAR looks like. In fairness, they moved the LAR on the tailwind of the subcutaneous octreotide. But LAR is octreotide with a polymer holding it together. And the reason that you have a "peppermint rush" when you take the shot the first time is because all of that octreotide on the outside of the spheres is released in the first 24 hours. Then it comes down to where the polymer beads start to slowly dissolve. That's why you sometimes have to start it with a sub-Q shot before you take the LAR, because you don't have any action for 7 days on your first shot. Now, Dr. Gene [Woltering] has done a big service by seeing how much these shots cost and who has to pay for them. Novartis doesn't charge a penny more than what they agreed to the FDA to charge. The

mixing of the drug by pharmacies or nurses is where it gets tricky, and it's the part that bothers me the most because it is a little difficult. You have to keep it at room temperature for ½ hour, then they have to put the solution in the vial very slowly, and if they do one of these things, it turns to rock because it's a suspension and not a solution. It reminds me of that advertisement on television where the guy goes into the kitchen, turns the drapes down, goes to the refrigerator, pulls the bottle out, and he looks at the bottle. It says, "Twist to open", okay? That's how you have to handle this medicine.

This is one of the most important slides in this talk. This is the Jim Howe slide where he went from 1997 with the SEER data and the National Tumor Registry Data and he put it together from about 1995 to when he presented this in 1999. And remember, when Sandostatin came into the United States it was 1989. Now, he is showing that the disease-specific survival isn't that 50% that Dr. Warner was talking about which we all knew, and it's not the 43% which was shown in these studies before 1990. It's 64 and 65% disease-specific survival regardless of overall size of the tumor, which is so important, as Dr. Warner showed you. Octreotide is therapeutic. Arnold from Germany is correct; it's not a palliative medicine, it's a therapeutic. As Dr. Kvols showed better than anybody in the New England Journal of Medicine articles way back in the 80s, it extended the median survival beyond 3 years. So, this is what you believe in and what it does for you. We need to have the receptors for that drug to work.

Finally, and this is the most exciting thing…OctreoTher; it's a clever name. Octreotide, OctreoScan and OctreoTher. Clever marketing. I also had an idea that Dr. Woltering knows about. When the FDA approved Sandostatin for secretory diarrhea, we had a cartoon made of a Rodin's "Thinker" sitting on a toilet and it said "Sandostatin: Get Them Off Their Seat and On Their Feet". Unfortunately, our motto never went anywhere. Now, this [on the slide] is OctreoTher and you can see it's a modified octreotide; there is a linker called DOTA, and there attached is a radio metal called yttrium-90. It has a very short wallop of about 1.2 cm and it's bound almost irreversibly to the link so it doesn't come off. Yttrium floating is bad for anybody, but not when it's attached and it binds specifically. Now how does it work? It's in the blood. It's going to the receptor. It goes into the receptor, and then poof….there it is. That's exactly how it works. Now, they say, "What does it sound like?" The only thing I can analogize it to is the first chapter of a Tom Clancy book called The White Mercedes. Do you remember the chapter where the two white Mercedes are going down the street, a truck comes alongside one of them, a flap goes up, they point a little tube with a bubble at the end of it and shoot at the Mercedes & it goes "puff" and the whole car is destroyed? That's the sound I think it makes; I just wanted to share that with you.

This [slide] is just the story of how the one thing that we've recently shown with the Phase II OctreoTher study is that the length and quality of life has improved. This is the same as what Dr. Kvols showed in the Phase I trial and the Europeans have shown. Paganelli has shown in Italy, Mackey has shown, Rotterdam has shown the same thing: there is a wonderfully clinically improved quality of life with the OctreoTher. That's the one thing that we can share with the world. The Phase II data is now being studied, and we're going to hear so much more from Dr. Kvols at the FDA. I just want to thank you very much for this wonderful opportunity and wish you all peace.

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