Carcinoid Tumors and Carcinoid Syndrome: What they are, how thay behave and how they are diagnosed

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Introduction of Dr. Richard Warner by Stephen Pazan:

Our first speaker today has been studying carcinoid cancer and diagnosing and treating carcinoid since the 1950s. From 1959 to the present he has been the principal investigator of the Mt. Sinai Medical School's study on the role of serotonin and the GI tract. He is Medical Director of the Carcinoid Cancer Foundation, Associate Clinical Professor of Medicine at Mt. Sinai School of Medicine in New York, and Adjunct Professor of clinical Medicine at Cornell. Last June, the New York Cancer Society and the Fund for Blood and Cancer Research honored him with the Catharine Margaret Pasmantier award for outstanding accomplishments and distinguished work with carcinoid and other neuroendocrine tumors. Speaking as a patient, he is a most thorough medical examiner while never losing his human warmth and humor. His wife, Monica, is famous among us as is her husband, especially for her Brobdingnagian - a favorite word of hers, I believe, work in the Carcinoid Cancer Foundation . They are both high-flying pilots in their spare time. Unfortunately, Monica was unexpectedly unable to come to this conference, but we are still very, very fortunate that her husband was able to come. Please welcome our first speaker, Dr. Richard Warner.

Dr. Richard Warner:

Good morning, ladies & gentlemen, friends that I know and friends I haven't met yet. My subject is very extensive and it covers a lot of ground. You of the audience come with all sorts of diverse levels of scientific and medical knowledge, varying from very little to very complex. In order to accommodate you all, I'm trying to be comprehensive. For those whom I am too technical for, please indulge me, and those for whom this might be over simplified, please indulge me, because we're trying to cover this for everybody. And I'm going to stick very much to the topics I've been requested to cover, namely what carcinoid tumors and syndrome are, how these conditions behave, that is, what is the normal course and how the course might be varied, and how we diagnose them. I'm not emphasizing or dealing with treatment. That is for the lecturers who will follow. Also, many of the slides or pictures I'm going to show you are fairly explicit and graphic. Some are of people, and you should know, of course, that anybody whose picture I show has given permission for their picture to be exhibited for educational purposes. So, let us continue.

It's only fitting that at the beginning of any lecture dealing with carcinoid and carcinoid syndrome, we show the hallmark of this rather rare disease, the intense flush. You can see on this gentleman's forehead where fingertip pressure blanched his skin
just the instant before the picture was taken. This is so characteristic of this flushing syndrome, although, as may of you know, the actual flush is not common, and only some 10-15% of all carcinoid tumors develop this.

Now, if we can go back a little in the history. Carcinoid is a relatively recent arrival to the medical

scene. In 1907, a German pathologist by the name of Obendorfer first described a group of odd little tumors in the intestine, which looked somewhat like cancers but also somewhat like truly benign tumors called adenomas. So, he gave them an intermediate name. Adenoma is a benign growth; carcinoma is a malignant growth. And he applied the term "carcinoid", which means like carcinoma but not quite the same.

So, with a concept with a relative degree of benignity behind it, these tumors arrived into the last century, and the concept of them being benign has unfortunately lingered. As time has gone by, we've seen that though they may be slow growing, they do have malignant potential, some more than others. And they represent a wide spectrum between very slow growing, almost benign and quite malignant. Fortunately, the majority are very slow, but we have learned that a significant number, maybe 20%, have a much more aggressive course and behave almost like ordinary cancers. This is a very important concept to maintain because I still get patients and get letters from people who say, "I was operated and they found a tumor in my intestine, tumors in my liver, and the doctor said I'm lucky it's a "benign" carcinoid". Well, it's not quite that benign. This concept of being so "benign" and therefore not worthy of treatment is one that has to be dispelled.

As the human embryo is being formed, along the back of this conglomeration of forming cells is a little ridge called the neural crest. That is destined to be part of the nervous system and other aspects of the developing body. From this neural crest arise certain specialized cells called neuroendocrine cells. These are the cells which, when dispersed throughout the body as this creature develops and forms, become neuroendocrine cells. They are the cells from which neuroendocrine tumors, of which carcinoid is the most common, arise. An abbreviation for neuroendocrine tumor is NET, so you may hear talk about NETs. Now, these cells have particular characteristics that allow them to be identified. When a biopsy is taken, the pathologist can perform certain staining on them and distinguish these from another type of tumor. If the standard stains are done, you can't prove that it's carcinoid or any type of neuroendocrine tumor cell. But, these cells have the ability to take up chromium when stained with potassium chromate, and so this ability to take up chromium led to the concept of the chromaffin cell. Often, carcinoid tumors are called chromaffinomas because they can take up chromium. They also have the ability to stain with silver salts, so they have been called argentaphylic and this is because the silver will stain these cells. Some of the tumors or some of the cells, depending on where they arise in the body, whether it be in the lung or in the intestine or in the rectum, have slightly different abilities, affinities, to take up these silver stains. Sometimes those differences can be taken advantage of in distinguishing where the tumor came from, because not all the time are we aware of where the tumor arises. We may find only metastatic deposits of tumor. To find the origin is, in my opinion, important because that helps to decide how to best treat the tumor.

Another concept or another aspect of the peculiarities of these neuroendocrine tumors, remembering that carcinoid is the most common of that family, is that they all are tumors which have the ability to elaborate endocrine products, hormones of one sort or another. So, the concept of amine precursor uptake and decarboxylation was developed and therefore became abbreviated as APUD. This means that these cells can take up amine precursors, these are amino acid Antecedents, and then change them chemically into other products. For example, in carcinoid, the cell has the ability to take up the substance which can be converted into serotonin, serotonin being the decarboxylated end result, which is an active hormone-like substance. Many of the endocrine products produced in the body are ultimately derived from amine precursors and so go through these chemical characteristics. Currently, advantage is being taken of this peculiar feature by adding radiolabeled substances such as carbon-11 to one of these precursor substances and then injecting it. The tumor cells will then take up this amine precursor labeled with, say, carbon-11 and hence be able to concentrate in the tumor and be shown, be demonstrable, on a PET scan. That's the basis for the carbon-11 5-hydroxytryptophan, or 5-HTP, PET scan that Dr. Öberg has been doing in Sweden. It's a very useful test but, at the moment, it's only available in Sweden.

Now, a word or two about the frequency of carcinoid. Originally, clinically significant carcinoids were quite rare. We have learned from various studies that there is a vast pool of clinically insignificant carcinoids. In other words, for every single carcinoid that causes symptoms and comes to medical attention, there are 2 to 4 more that haven't. Because they haven't caused any problems, they may last a lifetime and not at all come to anyone's attention. Sometimes these are found accidentally. At

any rate, in a study just published this past spring from Dr. Modlin's group at Yale, Dr. Modlin reviewed over the preceding five decades over 13,000 cases and came to some interesting statistical conclusions. First of all, over the past 10, 20, and even 30 years, every decade the frequency with which these tumors are being diagnosed has almost doubled. Originally, it was thought to occur in only 1 to 1 ½ cases per 100,000 per year in the United States. Now, it's up to 3 to 4 new cases per 100,000 in the general population. That means that 4,000 to 6,000 or more cases in the whole country are newly diagnosed every year. Of course, we don't know how many aren't diagnosed, but at least of the newly diagnosed cases, the incidence has increased. Since people live often for a long time with this disease, that means that we've probably got anywhere from 50,000 - 80,000 or more individuals walking around the country with carcinoid in whom the diagnosis is known, maybe more without a diagnosis. So, from an orphan disease, it's slowly moving into a category of a more frequent disease. Putting it in another perspective, most people have heard of Crohn's disease, an inflammatory disease of the bowel, which has received a great deal of attention and in which progress is being made in treatment. Carcinoid occurs at a frequency of about 50% that of Crohn's, which means it's not getting as much attention as it should.

I mentioned earlier the fact that carcinoid, as well as the other less common neuroendocrine tumors, are not as benign as was originally thought. In fact, 13% of all carcinoids that are diagnosed have distant metastasis at the time of the diagnosis. This is a sad fact which, unfortunately, many of you know. However, over the past ten years or so with the development of various drugs and improved diagnostic techniques, the pendulum of management which used to be exceedingly conservative - just "Wait and see because you may outlive your tumor" or "Be happy that you're lucky enough to have a slow-growing tumor rather than a more rapidly-growing one" and "Don't mess up your life by unpleasant treatment" - that pendulum of management has been swinging toward an earlier and more aggressive treatment. Now, of all the neuroendocrine tumors, carcinoid, as I said, comprises pretty nearly 2/3. The others are much less common such as insulin-producing, insulinomas, gastrinomas, VIPomas, somatostatinomas , glucagonomas, ACTH producing tumors and others. Many of these have some features in common that can cause diarrhea, for example, and they also cause other symptoms because of their particular endocrine products. Additionally, they look the same under the microscope unless you do special staining. Occasionally a pathologist will just say "neuroendocrine tumor - carcinoid" on the biopsy and just assume that it's carcinoid. It's not necessarily so. Specific stains have to be done to distinguish.

Now, of the carcinoid locations, the entire intestinal tract is the most common. Here [on the slide] you can see that, of those, the majority arise in the small intestine. Next in frequency, somewhat surprising, is the rectum. The next most common location is the appendix, which used to be thought of as the most common location. The appendiceal carcinoids are sort of special in that they rarely spread. I didn't say "never", but "rarely" spread. And when they do, they even more rarely cause the carcinoid syndrome, the flushing and the other features which I'll review for you shortly. The stomach is a special situation. Though it's not exceedingly common, it's common enough to require very definite consideration.

Stomach carcinoids come in three varieties. First, the most common is associated with atrophy, or withering, of the lining of the stomach as occurs in pernicious anemia, for example. In those instances, the stomach does not produce acid and, for a complicated chemical reason, carcinoids therefore develop in the stomach. These carcinoids are usually very benign, very small but multiple. In only 5% will these actually grow large enough to cause any trouble, and they can be cured very well by removing the end, or antrum, of the stomach. The next group of gastric carcinoids, which are very uncommon, is that associated with Zollinger-Ellison syndrome, or gastrinoma. A gastrinoma is a gastrin-producing neuroendocrine tumor arising in the pancreas or in adjacent tissues. The excessive gastrin is associated with the development of these little carcinoids. These tumors tend to be a little more malignant, but they're complicated in their treatment because often there are other endocrine tumors associated. And then the third type, which is a little more common, are solitary isolated carcinoids in the stomach, which behave very much like carcinoids arising elsewhere in the body and have a more malignant potential. At any rate, gastric carcinoids are grouped into three different types. It's important to distinguish which one it is because the management and the outlook will be different for each.

Next in frequency is the lung, or bronchial tree. About ¼ of all carcinoids arise there. This area is

particularly important because it can cause some other symptoms, respiratory symptoms, due to the mechanical presence of the tumor. Then, finally, there are a host of other unusual locations from which a very small number of carcinoids can arise. Some of these locations are very odd: the ovaries, the testes, the kidney, the skin, the biliary tract, and even the breast, and we've also seen a few cases where the wax glands in the ear have given rise to a carcinoid.

Here is a picture of a piece of small intestine containing a number of little carcinoid tumors. These small nodules (and I'm using this as an illustration because the intestine is the most common site for carcinoids, as I told you) are carcinoid tumors, and in 25% of the cases of intestinal carcinoids, they are multiple. That is, there is not just one isolated tumor, but rather a number of them. It can even be a dozen. And so, if the surgeon operates and finds a carcinoid, even a big one in the intestine, he's got to look in the rest of the intestine to make sure there is not one or more co-existing primary tumors. These may be present for years before causing symptoms, but even a small one (and this is a cross-section of one of these tiny little carcinoids), can be a time bomb. They arise under the mucosa, the lining membrane of the interior of the intestines. They have this sort of yellowish appearance, and this darker layer is the muscular layer of the intestine. You can see that this tiny little tumor has already got streamers of tumor cells eroding through, growing through, the muscle layer into the outer layers of the intestine, the serosa, and bulging it onto the surface. This tumor has invaded the full thickness of the intestine and consequently deserves to be treated like a regular cancer, having the whole thing removed.

Of all the gastrointestinal cancers, carcinoids constitute 2%. Those which have endocrine function, that is, can cause carcinoid syndrome, are called "functioning". Even before they have spread and grown large enough to produce enough substances to cause the features of the syndrome, careful measurements in the blood can show that they do produce the chemicals. The nonfunctioning ones and the functioning ones look exactly identical under the microscope; you can't tell the difference. What's necessary, again, to determine which type of neuroendocrine tumor it is, whether it's functioning or not, is dependent upon these special stains and the measurement of these special chemical products that they might produce. We call these special chemical products "markers"; they are biochemical footprints of the tumor. More on these staining features in a moment. Under the microscope, these tumors have very similar appearance with rather monotonously similar cells and very few mitoses. Mitosis is the term given to a cell when it's in the act of dividing, of replicating by splitting in two. Other cancers have increased numbers of mitotic figures (mitoses), so we like to have the pathologist not just diagnose it as carcinoid, but give us a count of how many mitoses are present. Therefore, we can have an idea as to the aggressiveness of the tumor. If it has beyond a certain number, it's no longer a simple, or what we call "typical", carcinoid. It then gets designated as "atypical" carcinoid, and that means a more aggressive tumor. If it's got more of these mitotic figures present than deserve to be for atypical, it then goes into the realm of being called cancer. It will now be called "neuroendocrine cancer". So, it's not enough just to have a diagnosis of carcinoid.

Now, into the clinical field. Again, as so many of you know, carcinoid is often misdiagnosed, especially carcinoid of the intestinal tract. Often it is thought to be irritable bowel syndrome (IBS) with vague digestive symptoms intermittently sometimes for many years. In other instances, it gets misdiagnosed as Crohn's disease, an inflammatory disease of the intestine. It can be treated as Crohn's disease for varying lengths of time, even years, until finally the progression of symptoms become such that surgery is required. Then everybody's surprised to find it was carcinoid all along. I've actually seen over a dozen such instances in the past year. And as we've said, it's less rare than we used to think. It's more malignant than we previously thought.

Traditionally, the points of origin of carcinoids were divided between what was considered the embryologic foregut, the midgut, or the hindgut. The foregut refers to those parts of the body that derived from a certain segment in the embryo, which includes the lungs, the upper respiratory tract, the thymus gland, the stomach, the duodenum and the pancreas. The midgut considers all of the intestine from the end of the duodenum on down to the middle of the colon. The hindgut is everything beyond that. There is a difference in the growth features of these tumors depending on where they arise. For example, the rectal carcinoids, while there are exceptions, unfortunately tend to be more benign, more innocuous, than the carcinoids in other parts of the body. And there also is a difference in response to some of the medications that might be used, depending on where the tumor arose. This is one reason why I like, whenever possible, to find the point of origin. Now, there

is a newer classification, and I only belabor you with this because you may hear about this as it is becoming more used, in which the classical serotonin (5-HT means serotonin) producing carcinoids in the intestine are the only ones to which the term carcinoid is applied. All other types would be called neuroendocrine tumors, say, of the lung or of the thymus or of the colon carcinoid type, depending again on where it arose.

Here again is this hierarchy of malignancy that I referred to before. Typical carcinoids are of low-grade malignancy. Atypical are of intermediate. Then, large cell and small cell neuroendocrine cancer are high-grade malignancies. There are some other groups where the neuroendocrine tumor cells are mixed in with ordinary-appearing cancer cells. Adenocarcinoid deserves particular attention because sometimes it's designated as goblet cell carcinoid, and that particular type of carcinoid has a wide variation in its degree of malignancy. Though, in general, the adenocarcinoma is a much more malignant tumor than ordinary carcinoid and so deserves more aggressive treatment.

Now, the special stains and features that help to predict behavior in terms of growth and therefore help to flavor judgment in deciding what treatment and how aggressive the treatment should be. We like to do a proliferation index; this is a special stain called Ki-67 or MIB-1, which stains the DNA material in the nucleus of the cell when it's getting ready to replicate. The more cells that stain positive with this, the increased rate of growth there is in the tumor. Sometimes other types of substances can be measured, various growth promoting factors and special markers such as c-kit which is a substance that is produced in varying amounts by a few of these tumors, but mean that the tumor is quite possibly going to respond to treatment with one of the newer targeted chemotherapies, such as Gleevec.

An interesting additional note is that 25% of all carcinoid patients will at some time in their lifetime develop another cancer of another type. It may have preceded the carcinoid, it may come during the carcinoid's known presence, or it may come after the carcinoid has been removed. The most common such tumors in men and women are carcinoma of the colon or, in men, prostate cancer, and in women, breast cancer. That means that anyone with a carcinoid has to be watched with increased surveillance for development of one of these secondary other type of tumors during their lifetime. Also, even if you have carcinoid, a new symptom or anything different has to be evaluated because it may be one of these other tumors. The standard exams, such as chest x-ray, colonoscopy, mammography, checking the PSA in the blood, all must be done.

Other observations: in 10% of carcinoid patients with metastases, that is, with tumors that have spread to a distant site, the primary tumor is not apparent. You can't find it. So, it's not an extraordinary event, therefore. There are three types of metastases; I'm referring to now, for example, to spread of tumor to the liver. There may be big lumps, nodules, that are easily seen or felt or imaged. They may be milliary, little tiny bumps the size of a grain of rice or match head, or they may be smaller yet, microscopic, that nobody can see and that imaging tests won't show. And it's not unusual, again, as some of you know, to have all the symptoms, all the appropriate chemical markers, and no discernible tumor, either primary or metastases. Such instances may be those in which there are only microscopic metastases.

Another feature of these functioning carcinoids that is very important is their tendency to stimulate dense deposits of fibrous tissue. A tiny tumor can be associated with a great deal of scar formation, fibrous tissue, in the abdomen. Or, in the heart, the valves of the heart become scarred by the deposits of this fibrous tissue, causing carcinoid valvular heart disease. This is something that occurs in as many as 50% of all carcinoid syndrome patients that's not always severe enough to cause symptoms, but it does occur and won't be discovered and properly followed unless looked for and suspected.

Now, the places that carcinoid likes to spread. Before I go over this list, I should say that there are several different degrees to which a tumor can extend. It may extend locally, regionally and to more distant locations. And the outlook, the prognosis, depends upon the extent of the spread. The first, especially for intestinal and also lung carcinoids, and again I'm emphasizing lymph nodes and adjacent tissue would be the first place it likes to go. But after that, the carcinoids from almost all locations would go mainly to the liver. Then, in the case of intestinal, they'd go to the mesentery (the membranes in the abdomen), the peritoneum (the lining of the abdominal cavity) and then to bone.

I've often been asked whether carcinoid can go to bone; it surely can. It may spread to the lung from another location, to the pancreas, to the skin , to the omentum (the fat pad that sits over our intestine in the middle of the abdomen), to the spleen, to the middle of the chest (the mediastinum), or adrenal glands. Even metastatic involvement of the heart can occur and does in about 5% of patients with distant metastases, and it's usually silent, not diagnosable, and may not cause symptoms. The brain is also involved in a small number of cases, kidneys, thyroid, testes, ovaries (sometimes in the ovaries and the testicles, carcinoid may start as the primary site), and the gallbladder.

In a very small percentage of carcinoid patients, the disease is inherited. There appear to be two different categories of inherited carcinoid. One is the MEN, or multiple endocrine neoplasia syndrome where it's genetically determined that this trait is passed on in a family. Or, there is plain familial carcinoid in which there is no true MEN syndrome, but a number of individual members of the same family will develop carcinoids.

I mentioned the absence of a primary tumor in 10% of the cases. It's very useful to be able to find the primary; I want to emphasize that point again. And since the majority of carcinoids arise in the small intestine, if the standard examinations (GI series, CT scan, colonoscopy, upper GI endoscopy) fail to show it, we're now picking up some cases where the primary was small and obscure by the use of wireless capsule endoscopy. That employs swallowing a tiny capsule, about the size of a vitamin capsule, which has a television camera, a light source, and a transmitter in it. It takes pictures, two every second, as it passes down through the digestive tract. Those pictures are recorded on a series of receivers that you wear like a corset. Then, after a day of this, this is plugged into a computer, downloaded, and the doctor can sit and watch moving pictures of that which this device has transmitted as it goes through the intestine. We have found a fairly large number of hitherto obscure primary carcinoids in the intestine by this technique.

Now, how does the doctor diagnose carcinoid? Well, the first thing is that you have to suspect it. If you don't suspect it, you won't do the appropriate tests and the only way you'll diagnose it is to stumble on it by accident, which does happen sometimes. But, if you suspect it, it's not that difficult to diagnose. For one thing, you can test the markers. Even if it's not associated with a clinical syndrome, there may be some of these biochemical footprints present in the urine and the blood, which will increase the likelihood of that being the diagnosis. Various imaging techniques are helpful, I mentioned CT scans and small bowel x-rays, chest x-rays. If the level of suspicion is higher, an OctreoScan and some of the newer PET scans, such as the one I talked about before, are all helpful. And finally, to confirm the diagnosis, we need a biopsy. That can be done in a variety of ways: needle biopsy, open surgical biopsy, biopsy taken at the time of endoscopy. All of these are ways to make the diagnosis, but the most important thing is to suspect. If you think of it, or if the doctor thinks of it, then he or she can do the right things.

As for the intestinal carcinoids, what are the most common presenting features? Abdominal pain. As I said, it may be intermittent, on and off, just a little cramping or indigestion for years. Or it may be that you're fine and then get a sudden and severe abdominal pain, as is often the introducing feature of this disease, with intestinal obstruction. Then, the person is operated on for intestinal obstruction and, lo and behold, there is a carcinoid. Obstruction, therefore, may be the presenting feature. In a few patients, bleeding may be the presenting feature, either heavy sudden bleeding that necessitates surgery, or intermittent bleeding for which no diagnosis can be found. In many of these cases, the wireless capsule has helped us to discern that it was from an intestinal carcinoid. In some patients, the disease goes without symptoms and they just end up with a mass that either the person feels himself and brings to the doctor's attention, or during the course of a routine exam, the doctor feels a mass. Then, the workup, the investigation, is initiated. And, in a very small number of patients, the features of the carcinoid syndrome - flushing or obscure diarrhea - are the main features that bring the disease to attention.

Now, as with most of these patients, if it's flushing, it's not the first thought that comes to the doctor's mind. If it's a woman of middle age, menopausal changes are suspected. If it's a paroxysmal thing, the patient may end up in the hands of an allergist and for some time be studied for allergy. It may be that a dermatologist sees the patient and diagnosis this as rosacea. Rosacea is a sort of wastebasket diagnosis that covers a whole host of underlying conditions, all of which are

characterized by a red face. And, if the face is red long enough, then the vessels become distended and there are skin changes that begin to develop. The skin coarsens and it gets labeled as rosacea. Actually, carcinoid syndrome can cause rosacea because of the chronic flushing, and so they overlap. At any rate, features of the syndrome may be present before diagnosis is made or a person goes to the doctor.

Now, let's deal with the manifestations of the carcinoid syndrome. The flushing is the hallmark, occurring in approximately 90% of cases. Next, diarrhea is almost as common. The diarrhea is usually painless; it may simply be somewhat more frequent bowel movements than one was accustomed to. I've had patients who say they were constipated life-long, only having a bowel movement every couple of days, and they began to have a daily bowel movement. "But that's not diarrhea" they would say. Well, not in the strict sense of the word, but it certainly represents a change in bowel habits and bowel pattern and that may be the first evidence of this condition. Or, the diarrhea may be profuse; watery stools, 10, 20, or a countless number in a day, enough to make the patient become dehydrated and have electrolyte disturbances.

Pellagra, which is a poorly recognized skin condition that is due basically to a deficiency in the vitamin niacin, can occur. And on rare occasion, in a very neglected person, the presenting feature, pellagra, is characterized by diarrhea of its own. And who needs that on top of carcinoid diarrhea? Pellagra is characterized by skin changes, a particular type of leathery change and pigmentation of the skin; I'll show you a picture of that later. It's also characterized by mental changes - forgetfulness, agitation, confusion - in far-advanced patients, so that pellagra may be the presenting manifestations and, indeed, mask the carcinoid syndrome. After flushing for a long time, venous telangiectasia, little red spidery aggregates of vessels, may appear in the face and a person may not be aware of that.

Bronchospasm, like asthma, may occur often as a late feature with wheezing, for example. Additionally, there are three types of heart manifestations. One is due to the stimulation of the heart by these substances produced by the tumors. The heart may just get tired; it may beat too fast and become exhausted, and so heart failure on that basis can occur. We can have metastases in the heart, as we said before. There may either be no symptoms or there may be interference with the conduction of the electrical signals that flow through the heart to keep it beating at a regular rate so we may have arrhythmias. Then, finally, the classic feature is this particular scarring of valves, usually the tricuspid and pulmonic valves. Those features cause heart failure with swelling of the feet and distention of the neck veins, which pulsate.

And, since most of the time it requires a large volume of metastases in the liver to cause this syndrome, there will be enlargement of the liver - hepatomegaly. Now, on the right side [of the slide] you can see there are a number of minor manifestations. They're not particularly specific for carcinoid, but they go along with the rest. Ulcers: peptic ulcer occurs in about 1/3 of the cases. Very low serum albumin, one of the protein contents of the blood, is present because the substances that make protein are being diverted by the tumor to make serotonin. There'll be an inordinate amount of wasting, atrophy of muscles, for similar reasons. There may be a lot of joint pain in some patients because there is a specific type of disturbance in the joints, and swelling of the legs in some cases. There may also be a disturbance in sugar metabolism. We may have a worsening of preexisting diabetes, or new diabetes appearing.

Here is a picture of the carcinoid flush - much like the one you saw at the beginning of this talk. And you'll notice that this man is intensely red, his face, his neck. And you see where fingertip pressure blanched the skin, his eyes are sort of swollen, and there is tearing. This is an acute carcinoid flush. It disappeared within a matter of a minute or two. And here he is, now, feeling obviously much better, but you see residual mask-like flush of which he is not even aware. Here is another gentleman who has had his carcinoid for a long time. You see fingertip pressure on his chest shows what his normal skin would look like. You'll notice on his cheeks these little red spidery patches; these are telangiectasia. Dealing with the skin, flushing, of course is the manifestation of carcinoid. Pellagra may be also, as I said before, causing a particular type of change in the skin of which I'll show you a picture. Scleroderma is an infrequent concomitant and it's a disease in which the skin becomes thickened and scarred. You lose the skin folds and you lose the elasticity in the skin. Scleroderma can also involve internal organs. And then, finally, you can have actual spread of

tumors to the skin so that little bumps may appear. Here is a picture of pellagra. You can see the glove-like discoloration and thickening of the skin of the hands and of the face, particularly the areas of the skin that are exposed to the sun. This is full blown pellagra. Here are some pictures of the skin with a host of little tiny nodules, these are carcinoid metastases to the skin.

Now, a word about serotonin metabolic pathways. Tryptophan, which is an amino acid that we get in our diet (we can't make it in our bodies), goes largely to form protein and nicotinic acid (niacin). But when we have a carcinoid tumor, it will go to form 5-hydroxytryptophan, or 5-HTP, which is the immediate precursor for serotonin. That in turn is converted to 5-hydroxytryptamine, which is another name for serotonin, (5-HT.) Then, the major, but not exclusive, breakdown product of serotonin is excreted in the urine as 5-HIAA, 5-hydroxyindoleacetic acid. We can measure all of these, and we often do.

The course usually, as we said before, is slow compared to other tumors, but it does proceed. In the intestine, overall about 20% will spread. The likelihood of spread is related mainly to the size of the tumor when diagnosed. The bigger the tumor, the more likely it is to spread. If it's between 1 and 2 cm in diameter, there is a 60% likelihood of spread. However, even smaller ones have the potential and occasionally do extend locally, to lymph nodes, for example. So, you can't say you're totally in the clear because it was a tiny carcinoid. The chances are, you are. But, you can't assume it. And I mentioned before that they're often multiple.

The carcinoid syndrome is very uncommon. As I said before, it occurs in no more than 10 or 15% of all carcinoids, slightly under 40% of all cases in the intestine, usually requiring liver metastases. In the untreated patient, and I emphasize that these figures are for those patients who have just been diagnosed but have not had any treatment. In the untreated patient, the average survival of a carcinoid without the syndrome, once a surgical diagnosis (a tissue diagnosis by a biopsy) is made, is 7 years. But, the range is very wide. There are some people who live many, many more years. And there are a few who don't live that long. Once the onset of symptoms occurs in the carcinoid syndrome, whether it be flushing or diarrhea, in the untreated patient, the average survival is 3 years. However, again, the range is wide. There is usually a 1-year delay in diagnosing carcinoid syndrome, which means that there may be only a survival of 2 years once the diagnosis is made if there is no treatment. Again, I emphasize the range is very wide, so you can't apply statistics to your own individual case since you don't know where you fit in the range.

This is a graph schematized by Dr. Vinnick, a long time ago, which emphasizes the usual slow growth of carcinoid of the intestine, changing into carcinoid syndrome. On the bottom of the graph you see years - it goes all the way up to 20 years - and then you see the red line indicating the course of the disease. You see for many, many years there are vague abdominal symptoms and it may be carried as irritable bowel. The tumor is slowly growing, eventually metastases occur well after 10 years. Then, somewhere along the line in the second decade, the diagnosis is established and the syndrome, the flushing and diarrhea, occur only very late in the course of this disease. Of course, as these progress, if the patient is not treated, he or she will not survive a long time.

I mentioned before that the prognosis is better with carcinoids from certain locations. Carcinoids originating in the appendix and rectum are the least dangerous. Next comes the lung, intestine, and finally pancreas. The pancreatic carcinoids are very uncommon, usually so-called "islet cell neuroendocrine tumors" are not true carcinoids. Only a small percentage, maybe 5%, arecarcinoids. The rest are either nonfunctioning or these other more rare tumors like gastrinomas and insulinomas. The size is important, as we said. The depth of invasion of the tissues at the time of diagnosis is an important determinant of survival. And, the microscopic appearance, the pattern of growth, is important. Patients with the carcinoid syndrome obviously have a worse outlook than those without the syndrome because they have both the growth of the tumor and the problems related to the effects of the circulating hormones on their different organs. Again, there is a wide variation.

What are the causes of death in carcinoid syndrome? This is not a very delightful topic, but one in which I know you're all interested. Fifty percent of patients with the syndrome, and I emphasize that this is with the syndrome, not a nonfunctioning carcinoid, 50% will succumb to cardiac complications; congestive failure or arrhythmias rank as the most frequent. Another 25% will die

from the results of the excessive hormones causing malabsorption that we just can't keep ahead of, electrolyte disturbances, bleeding, kidney failure, infections and so forth. Then the final 25% will die eventually from the actual spread of the tumors just as they would from other cancers. Good inroads are being made into this latter point by some of the newer chemotherapy agents.

Again, back to the diagnosis. We said that suspicion comes first, then examining the patient, feeling a lump or hearing a heart murmur, or seeing a flush. Then, after that, we look at the markers. If carcinoid is suspected, we can then measure the urine 5-HIAA, a 24-hour urine test. Certain foods and drugs have to be avoided because they can alter that test. We can measure the blood serotonin, which I like to do. And we can measure chromogranin A. Chromogranin A is another endocrine substance but is one which in itself doesn't appear to have much effect on the way the body functions. It's sort of the forerunner for other products that are more active, but it seems to be more constant and doesn't fluctuate as much as serotonin. It also is produced by nonfunctioning tumors, that is, a tumor that doesn't make lots of serotonin may nevertheless make an abundant amount of chromogranin A, so it's a good general marker. There are a number of noncarcinoid conditions that can also cause increased blood serotonin. Some of these are other types of tumors, neoplasia, and I've listed them here. I'm not going to over them one by one. The purpose is simply to show you that there are a lot of other types of things that can cause increased blood serotonin. Reliance on any one of these markers is not good enough. I like to do a panel of them.

Back to chromogranin A. It's about 90% of the time positive. It's stable; it doesn't fluctuate. It does seem to correlate with the size of the tumors, although not precisely. It is of some predictive value. A very, very high chromogranin A, I mean in the thousands, has a bad prognosis. And, most important, it's generally available. All major commercial laboratories can do it now. There are, however, a number of false alarms that can occur. Other conditions that can cause elevated chromogranin A: if you have impaired kidney function, impaired liver function, or if you're taking a proton pump inhibitor drug (PPI) - Prevacid, Nexium, Aciphex, Protonix. Though these are wonderful drugs, they inhibit the stomach acid very effectively, they elevate the chromogranin A. So, taking one of those drugs will get in the way. Eating will do it. If you've had stomach surgery and the end of the stomach hasn't been removed, that'll do it. If you have pernicious anemia, that will do it. Inflammatory bowel disease will elevate it, and so will physical stress or trauma. For example, a lady who was a marathon runner had flushing and diarrhea. She came in to me and her blood chromogranin A was very high. I made her stop running for a week and it went down to normal. So, all of these are possibilities.

There are secondary markers which aren't usually measured but can be. These are other substances I've listed here that are sometimes, in a minority of cases, elevated. So these too can be measured. Why test for these various markers? One, to confirm the diagnosis. Two, to evaluate the endocrine function of the tumor. This is because in a patient who has a carcinoid and no clinical syndrome who will undergo surgery, there is a concern that they can have an acute carcinoid crisis (flush and fall in blood pressure, for example) during the stress of surgery or anesthesia. You'd like to know that in advance and be prepared to treat with octreotide or give that to them before the surgery. If you've measured and found a high serotonin, you can at least know that's a possibility. Also, even though the diagnosis has been established, if you have this marker, you can follow it and gauge the progress of the condition. Finally, if there are other endocrine tumors, by measuring the different products, the ones I've shown you and others, we can get a clue to their presence.

Standard imaging techniques: I've enumerated them before and I'm not going to dwell on this. Just to show you, here is a CT scan. The dark areas at the lower left hand and the upper right represent tumors in the liver. Here is an OctreoScan. This is an isotope-labeled substance that is attracted to carcinoid and other neuroendocrine tumors. It normally is also attracted to the liver, the kidneys, the spleen and urinary bladder, which are represented by those darkened areas on the right and on the left. In addition, where there shouldn't be a dark spot, representing an accumulation of the isotope, there is. In the middle of the belly, here's one, here's another one, here's one down here; these are carcinoid tumors on an OctreoScan. Here's another OctreoScan and you see a dark spot here in the neck, up in the head, one in the chest representing metastatic lesion, and here's one down in the right thigh, a bone lesion. And here's another [OctreoScan] with multiple hot spots throughout the chest and those represent rib lesions. Here is an angiogram, an injection of a dye into an artery that goes to the liver. You can see on the left side a big, round ball, which represents a tumor with its

increased blood vessels. (Again, examples of various types of imaging.)

Finally, biopsy is necessary to clinch the diagnosis. Whether it be needle or whether it be an open biopsy, that is important. It's not enough to simply have the markers and the symptoms and say, "Ok, it's carcinoid".

Now, we will hear from the other speakers more detail about treatment, about newer advances and about other aspects of treating carcinoid and the syndrome. I've just listed here the three arbitrary categories of treatment: supportive, surgery and anti-proliferative. You will hear these features elaborated upon by those who follow.

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