

CENTER FOR MIND-BODY MEDICINE  
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CONCURRENT: Natural Angiogenesis Blockers

SPEAKERS: GEORGE BREWER, MD; RAYMOND CHANG, MD, FACP

COMMENTATOR: DOUGLAS WEED, MD, Ph.D.

MODERATOR: HENRY DREHER

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P R O C E E D I N G S

MR. DREHER: I'd like to start by saying that I am a medical writer specializing in complementary medicine for cancer. I am also an integrative cancer guide. I work with cancer patients, counseling them on their therapeutic options.

One of the things that I have found in my own research trying to help patients is that there is more and more interest in using natural compounds and non-toxic approaches to try and do something that mainstream medicine is spending probably billions of dollars trying to do; that is, to cut off the tumor blood supply.

Most of you, or some of you may be familiar with the term "angiogenesis." Angiogenesis means the swift development of blood vessels to feed a developing tumor. Tumor angiogenesis is actually the technical term for it. You may know about the work of Dr. Judah Folkman, who has pioneered the development of factors, most of them synthetic versions of molecules that exist naturally, to try and block and inhibit tumor blood vessel formation as a way of causing tumor regression, or at least stabilizing or stopping the growth of cancer.

So these anti-angiogenic strategies are being studied in major clinical trials. The drugs that are being used are very expensive. They are not available for most patients right now. There are some agents that are. But most of the most exciting new agents in clinical trials are not available to patients.

Meanwhile, there are a whole spate of natural products and non-toxic products that have anti-angiogenic properties. Patients are trying desperately now to piece together as much information as they can to begin to learn how to use these products to create a therapeutic intervention that actually does something similar to what these big drug companies and the National Cancer Institute and all these funders are trying to do in a pharmaceutical context.

So this session is devoted to looking into natural compounds that may have anti-angiogenic and may in fact be an important new part of the armamentarium for cancer, and particularly in a complementary medicine context. I know lots and lots of patients who are trying this.

It is my great pleasure to begin with an introduction of Dr. George Brewer, who is doing pioneering work in this area.

I'll tell you a little bit about Dr. Brewer. He graduated in pharmacy at Purdue, attended medical school at Indiana University and the University of Chicago, and received the MD degree in 1956.

After a residency in internal medicine, he joined the faculty at the University of Michigan, where he is currently Emeritus Morton S. and Henrietta K. Sellner Professor of Human Genetics and professor of internal medicine.

His current research interests are trace elements, particularly zinc, copper and molybdenum. He has developed zinc and tetrathiomolybdate, also known as tetrathiomolybdate, as treatments for Wilson's disease, and is currently working on tetrathiomolybdate as an anti-angiogenic therapy for cancer and other diseases.

Before I bring up Dr. Brewer, I'll say that tetrathiomolybdate is one of the most interesting new agents that lowers serum copper and therefore may have anti-angiogenic properties, and is being used for cancer patients as an anti-angiogenic strategy. Lots of patients are beginning to use this agent. And we have the man here, Dr. Brewer, who has really done the pivotal research in developing this area.

So it's my great pleasure to introduce to you Dr. George Brewer.

DR. BREWER: Thank you for the invitation. I think the work that we're doing does fit with this kind of thing, because we're using natural substances, zinc and molybdenum, and interactions with copper, of course, another natural substance in the body, to try to do some things about some diseases, including cancer. So I'm going to be using these kinds of slides and there is not a remote. So I'll keep needing to come back here.

I think these slides are going to be a little bit small for some of you in the back. I'll try to talk through them to a certain extent. Can we get it up a little higher? Put something under it?

PARTICIPANT: That's the best I can do.

DR. BREWER: You can make this lower though and then put that under. This doesn't make it bigger, huh? It's as big as it goes?

PARTICIPANT: That's as big as it goes.

DR. BREWER: Oh, boy. How's that? Okay. We're going to get going here.

I want to start by telling a story about how we got into this, because we developed treatments for this disease of copper toxicity called Wilson's disease. It gave us some good lessons for how to manipulate copper for other diseases like cancer. So we learned a little something as we went through this.

So this is an inherited disease of copper accumulation. It's fatal if untreated. It's pretty rare, but if you lower the copper in this disease, you can treat these patients very effectively.

When I started working on this, there were two drugs available, penicillamine and trientine, and they are pretty toxic. So I wanted to work with zinc, because we had some observations that zinc would do some good things to copper in the body. The way it works -- this is the small intestine. If you give zinc orally, it induces a protein in the intestinal cell called metallothionein, and the metallothionein has a very high affinity, or binding capacity -- strength for copper.

So once you induce this metallothionein with zinc, it then binds copper and prevents it from being absorbed. So it's a fairly simple process. You block the absorption of copper by giving zinc.

Now this is really a very effective mechanism. It sounds like kind of hand waving, but it's actually very, very powerful. As shown here, if you give a radioactive dose of copper, right here by mouth, and in a normal person, there is a ice spike within one or two hours in the blood of this absorbed radioactive copper. But if you give zinc, you completely block it. So it really is a potent blocker of the absorption of copper.

So we went on then to develop this as a treatment for this disease of copper poisoning -- Wilson's disease. We developed quite an experience for this rare disease. Probably over 325 patients treated by now with a lot of follow-up -- more than had ever been done with any other drug in this particular disease.

The FDA became convinced, and based on our research, approved it. It's called a new drug application for the maintenance therapy of Wilson's Disease. Now the problem here is that---What zinc does is it's a very nice leisurely de-coppering agent for maintenance treatment of these patients. But it's not so good for the acutely ill patient. So when the patient comes in, really copper-toxic, zinc wasn't very good, and the other drugs that were available made the patients worse because they mobilized copper out of the liver and into the brain and made them worse.

So I guess I didn't mention it, but this Wilson's disease causes damage in the brain and in the liver. So we needed a drug that would be faster-acting and non-toxic. That's why I began to work with this drug tetrathiomolybdate. It has a very interesting history that dates back to the early 1900s in Australia and New Zealand, where in pastures with a high level of molybdenum in the ground, ruminant animals, cattle and sheep, started developing a disease that turned out to be copper deficiency. They found that there is a lot of molybdenum in the soil. Of course, the grass picks up the molybdenum and the molybdenum gets into the cattle and the sheep and causes copper deficiency.

You could reproduce these in these ruminants by giving molybdenum. But if you gave molybdenum to rats, nothing happened. Later, some smart people figured out that the rumen, which is very sulfur-rich, actually produces a sulfur-molybdenum compound. So this is really a natural substance that is produced in the rumen of ruminates.

Tetrathiomolybdate is a molybdenum compound in which the rumen has added the sulfur groups. This makes it a very, very potent anti-copper agent.

The way this works -- it works differently than any of the other anti-copper agents like zinc and penicillamine, and so forth. It forms a three-way complex with copper and protein. So it isn't really a chelator like penicillamine, for example, which means that it directly binds a substance. But rather it's a complexor. The presence of this protein in this complex makes it behave somewhat differently, as I'll mention in a moment. But it's a very stable complex.

This copper then is no longer available for toxicity in Wilson's disease, and for tumors, when you're treating cancer. We give this tetrathiomolybdate with food, and there, it binds with the food copper and prevents its absorption. But if you give it between meals, it's nicely absorbed into the bloodstream, and there, it starts complexing with the copper in the blood, the available copper, with the blood albumin, and renders that copper no longer available, either for toxicity or, as we'll mention later, for use by tumors.

This is the first person ever treated with tetrathiomolybdate for this purpose. Some interesting things happened here. We did produce the immediate negative copper balance that I said we would. Then when we started giving the between-meal doses, look what happens to the blood copper. Instead of going down -- we're actually lowering the availability of copper in the body -- but instead of the blood copper going down, it goes up.

The reason is this complex of albumin is only very slowly cleared. So no longer is serum copper, blood copper, a useful way to tell what the patient's copper status is.

So we developed what we call a surrogate measure of copper status. It's a molecule called ceruloplasmin (CP). I'll talk a little bit about that in a minute or two when I start talking about cancer.

But this is a reason you can't use plasma copper to measure the body's copper when you're treating cancer patients. Next slide please. This patient, by the way, did very well.

We went on to treat by now 85 patients with tetrathiomolybdate with Wilson's disease. We had very, very good results; very low frequency of this neurologic worsening that is such a problem with penicillamine. 50 percent of the patients get worse if you treat them with penicillamine; very low percentage of our tetrathiomolybdate patients.

We're now doing a control study comparing it to trientine. Trientine has a sort of intermediate level of worsening. So tetrathiomolybdate is by far and away the best drug to treat these Wilson's disease patients with. Okay.

I believe that after 25 years of work with zinc and tetrathiomolybdate, that we've won a battle here with copper for this particular inherited disease. But then comes Battle II. It turns out that there are some very interesting effects of copper in cancer, and we have, as a result of developing these tools, have some weapons against that role of copper in cancer. So that's what I'm going to talk about now.

Henry mentioned that Dr. Folkman pioneered the idea of angiogenesis. This is a slide from a 1972 paper by Dr. Folkman. The idea is that a cancer cell can grow up to some little size -- he mentions about 2 millimeters, which is pretty small, and the cells inside this cancer mass get their nutrition by what's called diffusion; just coming in from the outside here.

If the tumor is going to grow, it has to develop a blood supply, and the technical term is perfusion of the cells. So that's the concept that Folkman developed; that if you could stop this angiogenesis, that would be an Achilles' Heel of tumors.

It's a really interesting idea, because adults don't really require angiogenesis except for wound healing and a few other particular things. So the tumor requires angiogenesis, but normal cells, normal tissues, do not.

The other part of this is that along about in the mid-80s, copper began to become involved in the angiogenesis story. Here was an early experiment, not by us, but by others. This is a rabbit cornea. And if you put a pellet in the rabbit cornea without any copper, nothing happens; whereas if there is a little bit of copper in that pellet, you get a prolific blood vessel response, a strong angiogenic response. So this is kind of a model.

It was used in experiments like this where half of the rabbits were made copper-deficient and half were not, and then an angiogenic substance put in the cornea. This one is prostaglandin E-1. You notice that the copper-deficient rabbits -- almost none of them had an angiogenic response, that blood vessel response we saw in the previous slide, where almost all of the controls did. So this showed that you could make a rabbit partially copper-deficient and slow down angiogenesis.

Then Dr. Brem, in the next slide, in the early 90s, took advantage of this and implanted tumors in the brains of normal rabbits. This is the one up here. You can see the tumor right there. Then copper-deficient rabbits. you can see how much less that grew. Really quite a dramatic effect.

This is a section through the brain of a control rabbit, and you can see the tumor here and the normal brain here. You see these blood vessels growing out. Compared to the next slide, which is the copper-deficient rabbit; no growth from the tumor out into the normal tissue.

Now, Dr. Brem, after what looks like very exciting results here, kind of got discouraged about this approach because there was no survival advantage. That was a little bit hard to understand at the time, but later, it looks like that all the rabbits developed edema or fluid accumulation in the brain and died from the brain stem being herniated at about the same pace, no matter whether the tumors are big or small. So he kind of left that field for a long time.

Meanwhile, we came along. Because I had developed this really nice potent drug, tetrathiomolybdate, very non-toxic, very, very potent, I got interested in reapplying that as an anti-tumor drug through the anti-angiogenesis, anti-copper approach.

You should understand that there is a hypothesis here, and that is that we all require copper. There is no getting away from the fact that we require copper. It is an essential trace element. But it looks like that there are two levels of requirement. One is up here that is required to support angiogenesis. The other one is down lower, so that you can drop that down into what we call an anti-angiogenic window, and the cells are still getting all the copper they need for making critical enzymes like cytochrome oxidase, and a few others.

So we call it an anti-angiogenic window. You can drop it down this far without interfering with these vital cellular functions and thereby avoiding toxicity.

I already mentioned that we can't just measure plasma or serum or blood copper because of this complex that builds up in the blood. So we have to use this molecule as a surrogate. It turns out to be terrific. This molecule is made by the liver. It's called ceruloplasmin. It's a copper-containing molecule. And the liver makes it, to the extent that there is copper available. So it's sort of acting like a tumor.

To the extent that copper is available, the liver makes ceruloplasmin. To the extent that copper is available, tumors can make blood vessels. So it's a great surrogate marker.

We find that if we drop it down no lower than about this level, we can prevent toxicity and get the patient into an anti-angiogenic window. Next slide please.

As I got into this, I teamed up with Dr. Sofia Merajver, who is an oncologist. I'm not an oncologist. Together, we designed a really very, very nice experiment. That's this HER-2/neutransgenic mouse study.

All of these mice with this particular genotype develop mammary cancers, breast cancers, by the time they are a year old. You can see that in this particular experiment, we started tetrathiomolybdate treatment in this group at 100 days. By the time we get out to 280 days, almost all of the untreated animals had developed breast cancer. None of the treated animals.

Here, we're giving this Tetrathiomolybdate by stomach tube once a day for 280 days -- weekends and everything. So it's quite a lot of work. But we were able to do it, and it really turned out to be a very, very beautiful demonstration of the potency of this approach. The next slide, please.

I want to show this slide because these are the control animals. I hope you can appreciate these large lumpy things here. Those are the mammary cancers in the control mice. This particular mouse has two. This is the treated animal. Nice and healthy and no visible tumors.

Now if you do sections through the breasts for these treated animals, there are little nodules of cancer cells there, just like Folkman predicted. Little nodules of cancer cells. You release this animal from treatment and they grow right up, just like these. So the cancer is there. It hasn't been cured, but it has been prevented from growing.

This teaches us some important lessons. That is, first of all, that it's a lot easier to prevent micro-metastatic disease from growing than it is, as we found out later, to go into a patient with a lot of tumor burden and try to stop all that metastatic disease from growing.

You can slow it down and you can halt its progression for a while, but it's a lot harder to permanently arrest it. Whereas with the micro-metastatic disease, it's really quite impressive what you can do. Next slide please.

I'm going to show you a variety of animal experiments just to show you that it's not just the HUR-2/neumammary cancer effect. This is a head and neck cancer that was implanted under the tongue of mice, and it grows very, very quickly. This is its natural environment.

Within 7 days, you have a lot of tumor in the control animals and good suppression in the treated animals.

If you measure the vasculature in this same experiment, you can see that this is a measure of blood vessels of angiogenesis. You can see the control animals have a lot. You have really rather markedly inhibited it with the tetrathiomolybdate treatment.

If you put this tumor into the flank of mice, it grows more slowly. This is about Day 54 here. It grows more slowly, and you get a very, very nice, again, suppression of growth with tetrathiomolybdate treatment. Okay.

Well, buoyed by the successful mouse work, Dr. Merajver and I started a clinical study, and it's now at 42 patients. A lot of the patients we call not evaluable, because it takes us a while to get them into this anti-angiogenic window, particularly in the early days, when we're kind of timid with the dosing in cancer patients. So we lost patients as we were initiating this study in particular.

But we ended up out of 42 patients, with 18 evaluable, in the sense that they got to the anti-angiogenic window long enough for us to see whether they had stable disease or not. It's a wide variety of solid tumors. There are 18 patients here, with about 11 different types of solid tumors. The actual freedom from progression at the time this slide was made, on average, was 10 months. With this kind of Phase I, Phase II study of advanced cancer, this is pretty good. Usually, this is without any treatment about 2 months. Some of these patients are rather impressive, like a couple down here. I'm going to talk a little bit more about them with breast cancer and sarcoma, who at the time this slide was made, were out 2 1/2 years and were out further later. So again, back. Yeah.

This is the patient with breast cancer who had really widely spread metastatic lymph node involvement and was treated for 30 months from the time this slide was made. She did have one brief course of herceptin, which made everything kind of melt away -- very impressive -- and then just maintained on tetrathiomolybdate.

Again, I think this demonstrates that if you can reduce the tumor burden, the anti-angiogenic approach is more effective.

This is a patient who is even more impressive. This is a patient with metastatic converse sarcoma all over the body, pretty much. She is still on treatment, out now 3-1/2 years with completely stable disease and just is living a very good quality of life.

Again, none of her disease was all that big at the time that we started therapy. It was widespread but not a huge tumor burden. This is a patient with renal cell carcinoma, and you can see a metastasis to a rib right here. At the time we started therapy and 3 months later, it's about the same size, but this after 3 months of therapy.

But we happened to be able to do what is called a blood flow-sensitive ultrasound in this patient. The color depicts the amount of blood flow, and you can see it was greatly reduced at the time the treatment had been 3 months along.

This is helpful because it documents that we're doing what we think we're doing; that is, stabilizing the tumor by either stabilizing blood supply or reducing blood supply. Okay.

This is a dog. More recently, I've gotten started on doing some work in dogs because I think they're going to help teach us some things. This is a dog with metastatic osteo-sarcoma, a greyhound. The dog had its limb amputated and had gone through the usual kinds of therapy -- various kinds of chemotherapy that are available in veterinary medicine.

Then we started with Bruce Maywell (?) at Davis a study of treating dogs with tetrathiomolybdate. This is the ceruloplasmin in this dog. Ceruloplasmins are a little bit lower in dogs than they are in people. You can see that by the time we got out to about 5 or 6 weeks, we had it under control. But now I want to show radiographs of the metastasis in this dog as we go through this course.

So this is a chest X-ray of the dog. I'm losing my light here. This is the lung. There is a metastasis right here which is called a cranial mass. It happens to be 8.8 centimeters. At the start of this study the CP is 8.5.

DR. BREWER: This is the ceruloplasmin. It's 8.5. The tumor mass that we're following, called a cranial mass, was 8.8. Now during the first month of therapy, we haven't gotten the CP down yet, and the cranial mass has grown. So this is showing that this tumor is rapidly growing. It's at 14.3 centimeters. And you can see how much bigger it is.

A month later, we have gotten the CP down. It's now 2.8. The cranial mass has stabilized at 14.4 centimeters. It's the same size as it was the month before. Then look at the next month. This is now 9.2 centimeters. Oops. Let's go back. You can see it's a lot smaller and it measures much smaller.

So actually, these metastasises are shrinking in this dog. At the same time it had a metabolic disease called hypertrophic osteopathy, which went away. It's a kind of metabolic disorder that comes on with metastatic disease, both in dogs and some humans. This dog has gone on and lived about 10 months. It was later euthanized because it developed urethral obstruction and developed renal -- kidney failure. But it's a really remarkable story in this particular dog. We have some other dogs now that have had similar results.

I think one of the interesting things that we're going to do here is rather than start now with dogs that have a lot of tumor burden -- this is osteo-sarcoma. It is always metastatic by the time you amputate the limb in the lungs. We're going to, right after limb amputation, start tetrathiomolybdate treatment. Just like the mice, the HER-2 mice. I think we can more long-term prevent the regrowth of these metastasises.

So in summary, tetrathiomolybdate, through an anti-copper, anti-angiogenic mechanism, based on our preliminary results, is a very effective non-toxic therapy for solid tumor metastatic disease.

I wanted to mention that there are other diseases, of what's called neo-vascularization -- angiogenesis is the same kind of term -- besides cancer. Those include diseases of the eye, such as macular degeneration, diabetic retinopathy, rheumatoid arthritis, and cirrhosis, as well as some other diseases.

We believe copper-lowering is a sort of a global anti-angiogenic -- has a sort of a global anti-angiogenic mechanism. One reason it may be working is that there are a whole number of -- a whole large number of angiogenic promoters that seem to be copper-dependent.

Next question. Why should that be? Why would copper? I mean, that's not true of zinc. It's not true of iron. Those are very important metals in biology. Why should copper sort of be generally related to these angiogenic? There are also growth factors that it's related to.

My theory about this is that in early evolution, copper was not as generally broadly available in the environment. Microorganisms learned to hunker down when there wasn't much copper -- not die, but hunker down -- and grow when there was a lot of copper.

So I think it became a primitive growth signal that we've retained right on up through mammalian evolution. So the next couple of slides show some of the people who work with me in Wilson's disease, particularly Dr. Merajver in the cancer work.

I'd be glad to answer any questions. I think there was one back there.

PARTICIPANT: I was just curious about the renal failure in the dog. Was it related to tumor -----  
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DR. BREWER: Nobody knows. I suspect there was a metastasis down there that eventually obstructed the ureter, but nobody knows for sure.

PARTICIPANT: Just a real quick practical question. Where did the funding come from for the HER-2/neu study?

DR. BREWER: Well, I've never had any specific funding for any of this work, except for Wilson's disease, from the FDA.

PARTICIPANT: Who ultimately paid for the research?

DR. BREWER: Dr. Merajver's lab has a grant from NIH. But I do believe we did the HER 2/neu work before that grant. So I think we sort of funded it out of our -- you know.

PARTICIPANT: University budget?

DR. BREWER: Yeah. You know, we get gift money. And we try to do what we can with what we have.

PARTICIPANT: I was intrigued by your statement that we don't need neo-vascularization as we get older.

DR. BREWER: Right.

PARTICIPANT: Of course, there are definitely normal physiological healing processes. It just brings to question, how long have you treated people, what's the longest, and have you explored --

DR. BREWER: 3-1/2 years.

PARTICIPANT: Okay. Have you seen any incidents or problems? I mean, what you're saying is you're talking about treating people at very early stages, for instance, that you might treat for --

DR. BREWER: Forever.

PARTICIPANT: 20 years, right?

DR. BREWER: No. We haven't seen any long-term side effects. There are some acute side effects. If you drop it down too low, you get into copper deficiency and the first thing you get is anemia, sometimes with leukopenia, because the bone marrow requires copper for cellular synthesis. But we've not run into any other toxicity.

PARTICIPANT: Have you supplemented with zinc treatments at certain points and used it --

DR. BREWER: That was my original idea, because I thought that tetrathiomolybdate was going to be kind of brittle. You know, in the Wilson's patients, you have all that copper. So it doesn't matter if the drug is real potent. I was really worried about it being very brittle in terms of control.

My original idea was to use tetrathiomolybdate and then switch to zinc. The tetrathiomolybdate worked so beautifully, we've never gotten around to switching to zinc, but it theoretically will work.

MR. DREHER: We'll take a couple more questions. Yes?

PARTICIPANT: What is the optimal level of copper in the blood, and how do you test an individual to see if they have that level?

DR. BREWER: You mean during therapy?

PARTICIPANT: Well, yes. Let's say to, like, just prevent cancer from -----

DR. BREWER: Well, if you're using this as a therapy or a therapeutic preventative, I guess, then we shoot for a ceruloplasmin of 5 to 15 milligrams per deciliter of blood; normal being about 20 to 40. We want to drop it down into that window of about 5 to 15.

PARTICIPANT: How can you test for that?

DR. BREWER: Well, it's a biochemical measure of ceruloplasmin in the blood. There are two or three different kinds of assays for it.

PARTICIPANT: This is what you called the CP?

DR. BREWER: CP. Right.

PARTICIPANT: Are these assays readily available? Can doctors get them?

DR. BREWER: Yes. A CP test is widely available. Yes.

MR. DREHER: A couple more questions. Yes?

PARTICIPANT: In a practical sense, are there physicians and oncologists using tetrathiomolybdate at this time?

DR. BREWER: Are there any what kind --

MR. DREHER: Physicians or oncologists using it now in their practice?

DR. BREWER: Right. Well --

PARTICIPANT: Or is it just theoretical and experimental? Is it actually --

DR. BREWER: The situation at the moment is that we have about 10 Phase II studies of specific cancers started at the University of Michigan.

One of them is at Wayne State University nearby. Then elsewhere, at Springhead -- it's not commercially available at this point. We're working with a company for the university to license it so that it can be developed more rapidly.

But there are little pockets of synthesis of tetrathiomolybdate out there in the country and in the world, and people are making it and they are selling it to people, and then people are using it.

The one precaution is that this drug is mildly unstable in air. So we only give prescriptions for 2 months. We've shown that it is adequately potent for that period. There is not that kind of control out there in the outside world.

Although if people call me, I tell them about it. It's in our papers, of course. So this company, if we sign this license, will find a way to stabilize it. I don't think that's going to be a huge problem.

MR. DREHER: I'd like to take one additional question. Then we'll come to more kinds of questions at the end, and we can ask Dr. Brewer additional questions.

Yes?

PARTICIPANT: Have you treated any HER-2 breast cancers?

MR. DREHER: Have you treated any breast cancer patients that are HER-2 positive? HER-2/neu breast cancer patients?

DR. BREWER: All right. The one that I showed you who had been treated 30 months was positive. That's why she was treated with herceptin.

MR. DREHER: Okay. I want to thank Dr. Brewer for an extraordinary presentation. I am really thrilled that we had Dr. Brewer here today. I think this is one of the most exciting developments that I've known about in the last several years, because it is a non-toxic agent. It has a clear mechanism of action. It has excellent research to support its validity and validated research to support its potential efficacy.

Just to elaborate a little more on what the question was over there. There are lots of pockets of use of this agent in the country. There are cancer patients throughout the country who are using tetrathiomolybdate.

I don't know how they are getting it. But they're getting it. I know of some clinicians who are prescribing it for their patients. Dr. Chang may have some more insight about this issue, if he wants to address it. But I thank you all very much for listening.

Now I'm going to introduce to you our next guest, Dr. Raymond Chang. Known for his expertise in traditional Chinese medicine and his innovative approach to integrative care. I should probably have this too for your introduction. Hold on, then I'm going to switch it over to you. Let me start over with Dr. Chang.

Known for his expertise in traditional Chinese medicine and his innovative approach to cancer care, he received his MD from Brown University and was Kaiser Fellow at Cornell University before joining Memorial Sloan-Kettering Cancer Center from 1987 to 1997.

Dr. Chang is currently assistant professor of Medicine at the Albert Einstein School of Medicine and directs an alternative cancer program in New York. He is president of the Institute of East-West Medicine and chaired the First International Asian Therapies for Cancer Conference in 2001, and serves on the editorial board of the PDQ database of the National Cancer Institute, Journal of Alternative and Complementary Medicine, and clinical acupuncture at Oriental Medicine.

I want to add that Dr. Chang is one of the most innovative, clinically courageous in some ways, integrative cancer specialists in New York, where I live. I know I refer a lot of my patients to Dr. Chang and many of them have done extraordinarily well with his creative yet cautious approach to integrative cancer medicine.

So it is a great pleasure for me to introduce to you Dr. Chang, who will present you a very broad overview of the kinds of natural compounds that have anti-angiogenic properties and may have relevance to cancer therapy.

Here is Dr. Chang. Thank you.

DR. CHANG: Thanks, Henry, for the kind introduction. I also very much appreciate Dr. Brewer's giving this background about angiogenesis.

When Henry asked me to do this, he had the topic in mind, and I'm just so thrilled that he was able to introduce this topic to this particular CAM conference that's hosted by CMBM.

But you realize that the topic is very large and the field is complex. There are easily four dozen drugs currently in clinical trials that are anti-angiogenics.

I started using anti-angiogenic therapies actually quite early on with the help of Dr. Folkman. We had patients -- he doesn't treat patients, but I have patients who went to him privately in consultation a few years before any of the actual drugs went into trials.

We had done originally one case, compassionate INDs, with some of the very original anti-angiogenic therapies with approval from the FDA, from the hospital's IRB, et cetera, et cetera, on very difficult cases. This is, again, several years ago.

We did it actually in combination with chemo at a time when nobody had combined it with chemotherapy. And the FDA seriously questioned whether it was safe to use some of these new agents - - these were new drugs -- combined with chemo because there was no data.

But we sort of went through the process and pleaded the cases on individual grounds, and were able to do some very interesting work that I think also helped Dr. Folkman's group to understand some of these things.

I think everybody appreciates that the combination; that anti-angiogenics and chemotherapy may be the wave of the future, as all the new trials are now designed that way.

We also used Thalidomide, which is now approved, not as an anti-angiogenic, but originally approved for leprosy. We used it before it was approved, or reapproved in this country, shall I say.

I remember having sent patients to all sorts of places. I had sent patients to England, where it is available. I had sent patients even to Haiti, where it's available. It's certainly available in Brazil. For a while, it was available through buyers' groups for HIV patients, except the FDA shut those down. They were in California. They were closed down. They are still closed down.

Of course, subsequently now, Celgene makes Thalidomide which then we happily prescribe. But anyway, this is a very large area. We're going to try address it in 30 minutes.

For a very large area, I chose to use the minimum of slides. I have actually done very few talks with so few slides. But we'll try to do that. Let's start with the first slide.

For those of you who are interested in this field, I did provide you with a lot of references. So it's in that supplemental handout. I don't know which particular chapter, but there is a summary, there are take-home messages, and there are pop net abstracts so that people who are interested can follow through with this.

But you need to first understand that angiogenesis is very complex matter. It is not a single key, a single answer, a single pathway. There is no magic bullet in this, I don't believe. I think that may be one of the problems with the trials now is, you know, that clinical trials of drugs -- I think except for Dr. Brewer's Phase I that was published in 1999, late 1999 or early 2000 -- presented in late 1999, there is nothing that is so dramatically exciting that we can see on the horizon.

A lot of people have been discouraged, partly because there was over-hype of some of Dr. Folkman's drugs. So I think some people are disappointed.

But I think probably the reason why is the fact that there is a lot involved in angiogenesis. It's not a simple pathway. It's not a single pathway. There is the involvement of gene expression. There is the involvement of enzymes, proteinases metalloproteinases. There are multiple ones. There is the involvement of signal processing. Then, of course, these trace elements.

I think it's very interesting, for example, copper doesn't act at one particular location. It is not like a molecular treatment, a targeted molecular treatment. But as a co-factor, it plays a role in multiple parts of this whole scheme.

So it is very important to realize that there is such complexity involved and therefore, all these things can be targeted. So that's one take-home message.

This is going to be a problem. Okay. There is actually a site where you can find the new drugs that are being trialed, listed by the NCI. There is a home page for anti-angiogenesis. If you look into the NCI Web pages, they list the mechanisms of how things work.

There are metalloproteinase inhibitors. One early one, for example, is the British ----- Marimastat, that didn't do so well. It was in trials. It may still be in trials for lung cancer, et cetera.

There is inhibition of endothelial cells. There is direct blockage of activation of angiogenesis. There is inhibition of signaling. Then there are other so-called non-specific entities.

All together, there may be 20 or so anti-angiogenic drugs in trial that are listed. That list is not up to date. It is at least a year behind. If there is somebody from the NCI here, they may have something to do, to update that list.

But *Nature* had a more recent article, and I didn't have it in the reference. But it gives this map of all these pathways and shows where each drug is acting. It's a very complicated map. It's a nice overall review.

It also then lists the drug companies with their drugs that are in trials. So there are drugs. There are drugs in trials for this. There are natural agents. But a lot of drugs derive from natural agents.

So partly, when Henry asked me to talk about natural treatments, I mean, nature -- how to define what is natural and what is naturally derived? A lot of treatments are no longer natural because they became drugs, so we don't classify them as natural.

But the classification of what is a drug and what is not a drug. Tetrathiomolybdate can be considered natural, yet when it's approved as a drug -- well, it is a drug in a way -- it may no longer be considered a natural substance. So keep those rough distinctions in mind and then we just use them to help us understand what the field is like. All right.

Again, before going on further, you need to realize that there are so many anti-angiogenics from nature. It's very interesting to note that they don't come from any particular class of agents or particular class of natural agents. It could be any of these things. There are agents in all these families that have been shown to have anti-angiogenic effects to various extents. Sulfate of polysaccharides, a prime example of which is heparin --

PARTICIPANT: What? Heparin. These are specifically linked sugar molecules that are highly negatively charged, anionic saccharides that are biologically active and they are derived from nature.

Heparin is found in the internal organs of mammals; it's from the liver, from the intestine. It was originally from scientists at Connaught that had first discovered it. They also discovered insulin, by the way, I believe, in the 20s or 30s from liver -- in bovine liver, and that's where it's isolated from.

Many such sulfates and polysaccharides in the heparin family are anti-angiogenic. Mayo Clinic has -- had -- I don't know what the status is currently -- a Phase II trial of using heparin, low-molecular weight heparin, because of reduced side effects, for the treatment of solid tumors. It was a Phase II trial, and I don't know if it's currently active, but I am aware of such a trial.

And Dr. Folkman was intensely interested and still is, in the use of such sulfated polysaccharides. I include one abstract of a paper which was published by Dr. Folkman's group on the use of heparin or the nature of heparin.

And he did treat one pediatric case. Dr. Folkman himself is a pediatric surgeon, for those of you who don't know him or his work. But he did treat a case of a young girl with an angiosarcoma with heparin, and it responded very nicely, with a large tumor on the face regressing over a period with -- I'm sorry, it's a combination, actually. I should correct that; it's with interferon.

So that is very interesting. And a lot of these things do come from nature, as I mentioned. There are snake bites that contain -- because these things, when nature -- polysulfates -- saccharides or sulfated polysaccharides, because of the high negative charge, they are, by and large, toxic in the sense that they are anticoagulants.

And, therefore, you can find these things in certain reptile poisons, because when a snake bites, it needs to prevent coagulation to allow the snake to feed. So a lot of the saliva from certain reptiles, for example, contain these things, and that can be a source of sulfated polysaccharides.

Now, polyphenolic compounds, to actually make it very simple, it's tea that's the one good example, green tea. The same phenols are found in even simpler things such as chocolate.

Green tea is widely used and consumed, and there is good epidemiologic data, which we shouldn't get into here, that is useful in preventing certain cancers. There are people who have tried to use it as a treatment for cancer.

There was a trial, again, a Phase II trial, that was at Sloan-Kettering, Dr. Ang (?) and Dr. Crusicsera (?) have used it to treat lung cancer and other cancers, but in concentrated form. But because of side effects, I think a lot of patients cannot really attain the 50 cups a day level of green tea that was intended in the trial.

But it was subsequently found -- this is after we know how that green tea may reduce the risk for cancer and we know that there are other properties from green tea that inhibit cancer cell proliferation and induces apoptosis; there are other anti-cancer mechanisms of green tea or of tea.

And the catechins from green tea, all the polyphenolic compounds from green tea were subsequently, quite late in this whole development, was found to be anti-angiogenic. So after the fact, it was known that green tea could be anti-cancerous. It was found to be anti-angiogenic, so that's interesting.

But another interesting property reflective of many, many natural anti-angiogenics is that they have multiple pathways of functions, that they do not -- they're not only anti-cancerous because they are anti-angiogenic -- green tea is a good example; soy is another example -- that there are other things that these compounds do that will help control cancer.

Sterols: I think a prime example of that is what's already developed into trials. The Magaynon (?) Company makes squalamine, which is currently in clinical trials, and I believe there are abstracts on that. And the company website lists a lot of literature. Squalamine is a sterol that's derived from the liver of the shark species, squalus.

It's used; it's been in clinical trials. It's actually, also, I think -- I think Dr. Brem may have also studied that one for brain tumors also, and it was also presented by Hopkins as in animal models, useful for brain cancer. It's in trials for several different cancers. Currently, I believe it's Phase II or Phase II/III.

There is some toxicity at high dose. It is given intravenously, and it's a continuous IV infusion for five days every three weeks. So it is not just oral shark liver, the shark liver oil, if you will. It has to be given intravenously, but that's an example of sterol being used.

Fatty acids, that's interesting. That's commonly in use as a complementary modality, vitamin modality for treatment of many things, from arthritis to PMS, et cetera.

Now, which fatty acids are we talking about? Specifically, there is data for the omega-3 fatty acid, DHA, and for the omega-6 fatty acid, GLA, that it has anti-angiogenic properties. Fish oils have been implicated. EPA, I've not seen a study on EPA, particularly, but fish oils which contain DHA have been implicated as useful as anti-angiogenic at the laboratory level. So that's fatty acids.

Then some vitamins are very interesting. Vitamin A, Vitamin D-3, these are potent, well-known, the retinoids and the Vitamin D-3 family. These are potent and well-known inducers of cellular differentiation, and therefore, apoptosis.

They are used clinically as drugs. There's a lot of research now on derivatives, more potent derivatives, less toxic derivatives of both retinoids and Vitamin D-3 analogues for the treatment of cancer, particularly hematologic cancer.

Now, it is interesting that there is good research -- and, again, I have included that material in the handout of some of this, the D-3, for example, the research on that. But it's easy to find yourself on Pub Med, if you're interested. But they are also anti-angiogenic, so again, this fulfills this -- what I was saying earlier, that many of these natural compounds have multiple anti-cancer capacity, if you will. They don't

act in any single modality. They may be anti-angiogenic, but they have other anti-cancer properties as well.

Micronutrients: Professor Dreher had mentioned a couple. It's interesting that selenium has also been studied, and been found -- I believe we have included an article from the ANC Cancer Research Center in Denver, demonstrating that monomethyl selenium specifically inhibits VEGF, vascular endothelial growth factor, which is one of the key factors that we're targeting in anti-androgenesis treatment, as well as MMP-2, which is a metalloproteinase that is involved in androgenesis, that monomethyl selenium inhibits androgenesis in this fashion. So there are other minerals that are of interest.

I also take some interest in zinc. There is work showing that in brain cancer, for example, that the ratio of copper to zinc is important. I think Professor Dreher is much more qualified to comment on that, whether zinc, independently, may have some usefulness. Zinc is a co-factor in many of the proteinases and the metalloproteinases.

So whether it's more than just copper, but a ratio of copper to zinc, it may be that that is important. They have found that there is very high copper-to-zinc ratio in the brain tumor cells versus otherwise normal neuronal tissue, so I think that that's interesting.

Now, there are other things which do not fall neatly into any of these categories; for example, melatonin. Now, as you well know, melatonin has many publications, mostly from Europe, from the Sonis (?) Group out of Italy. Again, I think they pay it more respect in Europe, because it is a drug.

It's a hormone, and it is a prescription over there, whereas here, it's a 7-11, what I will call 7-11 -- it is like everybody, you know -- Vitamin Shoppe. So there is very little respect for melatonin.

There was a lot of worry before from breast cancer oncologists about melatonin, but really the overwhelming research, if you read -- and there's a lot; there's easily 800-900 papers on melatonin and cancer -- that is quite useful; that it inhibits breast cancer.

Several days ago, there were new reports of women who are night-shift workers who are at increased risk for breast cancer because of low melatonin levels, and also applies to airline stewardesses, et cetera.

So melatonin has broad-range, I think, broad anti-cancer activity, not only because -- at a hormonal level, but it's also been found, again, in work published by the Sonis from Italy, that it's anti-angiogenic. But melatonin does not fall neatly into any of these categories.

So what is the message here? Well, the message is that natural anti-angiogenics can come from almost anywhere; that there are a lot of things that we commonly use, as commonly as things that we eat every day -- fish, tea, and soy, et cetera, flavones. Red wine has resveratrol, which is also anti-angiogenic -- grapes. There are a lot of these things that are anti-angiogenic, but of course, the ultimate question is, so what?

I just want to give you all the natural -- what the field looks like. Back, okay. Now, a lot of the natural things, as I said, there is this unclear distinction, what is natural and what is a drug.

And I don't want to get into that too much, but a lot of drugs that originally came from nature, but are now classified or being studied or being trialed as drugs, they do come from nature, and in that way, can be considered natural, naturally-derived, and have anti-angiogenic activity.

Heparin, I mentioned; suramin is from urea. Suramin was trialed. It's also a highly negatively charged polysaccharide, but it has a lot of side effects. Bleeding is a major problem with suramin, so this is no longer being trialed. It was being studied for prostate cancer, et cetera, as an anti-cancer drug. It's dropped out the way.

Now, taxol, as mentioned, taxol is interesting as chemotherapy, of course, but it is from nature in the sense that it comes from the Pacific Yew tree, the bark of the Pacific Yew tree, so in that way, it is naturally derived.

At low doses -- and it's not only taxol but several low-dose chemotherapeutic drugs, low-dose chemotherapeutic drugs, because it targets endothelium at the low concentrations. It becomes toxic to the lining -- the vascular lining, and therefore, it inhibits the blood supply. The blood supply needs to grow, too, in angiogenesis, like cancer has to grow.

So if chemotherapy administered at a lower dose hits the vascular supply and is toxic to the vascular supply, that can be used as an anti-angiogenic, and that is well-demonstrated, I think.

For those of you who are interested, if I didn't put an actual reference down, there is a journal called "Cancer and Metastases Review." And there's one volume that reviews this whole area of using chemotherapy as anti-angiogenics, something that's very interesting, low-dose chemotherapy.

Of course, low-dose chemotherapy as a cancer treatment is practiced in Europe and some German clinics, for example.

Interferon, again, that is broad-based. As you know, it is an immune stimulant. It has broad-based activity, and that is used as an anti-angiogenic. It is listed as one of the drugs that's currently in trials as an anti-angiogenic in the NCI site that I mentioned.

I should correct myself: Dr. Folkman actually, for that angiosarcoma case, used interferon, not at very high doses, three to six million units, subcu, every day. It's not a very high dose; it's quite tolerable, okay?

Now, a lot of people have heard of shark's cartilage. I didn't mention it too much, because it's quite well known. That's the way it was marketed when it first came out -- sharks don't get cancer, because in the shark's cartilage, there's no vascular supply, and there's something in shark's cartilage therefore that inhibits angiogenesis, and that's well-demonstrated, originally demonstrated, actually, by Dr. Folkman and group in the 70s, I believe. And it was published in "Science," and that was used, actually, to Dr. Folkman's consternation, for marketing purposes, I think, for some of the shark cartilage products that are out there.

As a treatment, it has -- the popularity of shark's cartilage has waned substantially. In the past few years, I've noticed that, but you should be aware that several biological entities from shark's cartilage have been isolated and patented.

And there is development of shark cartilage as a drug, in the sense of being developed as a drug, and it's currently in Phase III trials against non-small cell lung, multiple myeloma, and renal cell cancer, both in Canada and in the U.S. as a drug; this is an oral agent, and it's derived from shark's cartilage.

Squalamine, I talked about somewhat. Okay, 2ME is also out of Dr. Folkman's, and it's currently being developed by Entremed, the same people who developed angiostatin and andostatin. It is a derivative of estradiol; it's 2-methyl-estradiol. It's a derivative of estradiol and it's pretty nontoxic.

There's a lot of research on it. It's an old compound, and, again, it's very easy for you to find information on it if you want to. But estradiol, being a natural hormone in women -- I have listed that under nature-derived anti-angiogenics.

Then there is combrestatin, which is from *Combretum caffum*; there's angiostatin, et cetera, which is an endogenous protein. I have highlighted some things which are in trials, such as squalamine and 2ME; some things are available.

This is just for us; you don't have to have the details of all these drugs, et cetera, et cetera, but just to highlight the complexity of this area, to show you that there are a lot of agents that are anti-angiogenics, and it depends on how they classify them.

Now, these are some of the supplements. Some of them, we mentioned, but these are supplements. This is what we generally mean, more to be naturally derived, but these are some of the supplements out there that are anti-angiogenics, and some of them are interesting.

Licorice. Well, licorice is also a Chinese herb. Again, this is a matter of classification. We start from down here to Chinese herbals, and tripterygium is actually, in Chinese, is *leigongteng*, which is the thunder god's vine. It's used and quite well proven, very well proven as useful for rheumatoid arthritis. It's an immune suppressant, interestingly, tripterygium.

But there are others, and there are formulas, et cetera, so this would be a whole topic in itself, which I don't want to get into.

But some of the common things, you know -- Vitamin E, there is one study that I have found; lactoferrin is interesting. It's an orally-available agent derived from milk, and I don't know, but I think it also requires -- it may require copper -- or iron, I'm sorry -- includes iron as part of the molecular structure. And this is also interesting, because it's available in the health food store and has shown to be anti-angiogenic.

The Scandinavians are the people who have done research on this. The publication is from Scandinavia.

Curcumin is interesting. There's quite a lot of research on curcumin. It's a COX-2 inhibitor. As you may know, there's a whole big field now with COX-2 inhibitors being anti-angiogenic. Celebrex, at high dose, has been approved in late 1999, I believe, by the FDA, as a preventative for colon cancer in those who are at high risk because of hereditary colonic polyps, adenomas. It is now in trials.

At New York Hospital, for example, it's in trials for lung cancer; it's in trials for breast cancer; it's in trials for brain cancer, high-dose Celebrex as a COX-2 inhibitor. And Celebrex, by the way, has other anti-cancer mechanisms.

But curcumin contains -- it's a spice, if you don't know what curcumin is. Curcumin is a spice from tumeric, so it's in curry. The yellow pigment in curry -- and there are many, many kinds of curries with different portions of different spices, but the yellow pigment from curry, the biologic part, is from tumeric, from which curcumin is derived. And curcumin has anti-angiogenic activity because of the curcuminoids that are in it.

There are other kinds of cumins. There's black cumin; nigella (?) is another herb. The research, I believe, is from Southern California.

There are other similar -- the family of cumins, if you will, that have anti-angiogenic activity, and it's not surprising.

Alkylglycerols, which are similar, the aminosterols, also from shark liver oil, but this is available as a supplement, as a vitamin, if you will, a supplement, as a natural supplement, so this is what's available.

And I mentioned green tea, retinoids, DHA, GLA, soy genestein isoflavones, and there are other flavones or flavonoids like resveratrol; these are flavonoids, other flavonoids, and all these have been demonstrated to be anti-angiogenic, at least in the laboratory.

So there are a lot of these agents that are quite available to your patients, et cetera, that are not unapproved drugs or drugs that are in trials, et cetera, et cetera.

Next, I believe, is the final slide. And, again, there are a lot of question marks. There's a problem. As I told you, since there are so many natural anti-angiogenics, and some of them are simple things, as your glass of wine, your piece of tofu, your miso soup or your cup of green tea.

Where does this all get us to? Well, there's an issue. I mean, there are many assays and there are pros and cons of the assays for angiogenesis. Those people who do the actual assays -- and I used to do them, too, actually, with Dr. Shi (?) at LIJ, where we tested originally some various materials.

But the assays are finicky. We used chicken embryo on the early days, et cetera, but it depends on how you set things up. You can get effects and you can publish it and say there's some evidence, in vitro evidence, on models from either cornea or chick embryo, et cetera, that there is, so it's not clear what the actual strength is.

How many cups of tea? Okay, tea is anti-angiogenic. Soy is anti-angiogenic. How much soy? It's the same issue with a lot of chemopreventatives.

You know, the cruciferous vegetables are useful for preventing breast cancer. But we know that. You know, indole-3-carbinol and di-indolymethane, et cetera. But how much are you supposed to eat? Two pounds of cabbages and cauliflowers et cetera a day, which is not achievable?

How much salmon to eat to achieve the omega-3 fatty acid et cetera to that level? So this is a big issue. These are related. We don't know really the relative strengths. It's hard to compare.

We don't know the doses, because, again, you will find that most of the studies are not at a clinical level. They are not done in humans. Most of the proof or the implication of anti-angiogenic activity is in vitro work based on models, and, at best, animal work, but certainly not clinic work.

But as we know, this does not translate. You cannot extrapolate laboratory and animal data into humans. However, I think that it is certainly true and logical that in a complex process such as angiogenesis, that it's reasonable to combine.

I'll show you very early on that there are angiogenic pathways at different levels. Okay? Things which stimulate angiogenesis, which stimulate -- that effect signaling, that effect the proteinases and the metalloproteinase.

It is reasonable and logical to combine a class of anti-angiogenics and use them rationally and use one, at least one, from each category. That makes sense. That that is probably an optimal anti-angiogenic cocktail, if you will.

It's interesting that copper reduction works that well because copper in itself has a -- it's not a cocktail, it's one thing. But it participates in a cocktail of activities. That may be why it works so particularly nicely -- at least from the Phase I and the anecdotal cases.

It is certainly useful to use these natural agents during chemo and radiation, I think, because good data now is coming out -- a lot of the trials that you see, you know, with the Thalidomide trials, a lot of the newer anti-angiogenic trials are being done together with chemotherapy at the same time. Because I think there is a synergy zone, and there is -- without going into too much about what really is going on when there is Cox-2 inhibition, but the Celebrex, it is very well-demonstrated -- let's go to Celebrex -- that as a Cox-2 inhibitor, it is synergistic with gamma radiation, and it is also synergistic, which means you get better results, it's more than additive when given together with certain chemos.

5FU particularly has been studied with Celebrex for example, showing that combination is better than each one alone. Since the natural things, some of the stuff that we talked about, the green teas, the soy, et cetera, is fairly non-toxic and inexpensive, it's reasonable to use these things as preventatives. We need trials. I mean, ultimately, I think that is what is going to -- at least to prove certain principles, et cetera.

It's easy for me to say -- and there is only one word here -- but it's not easy to do because funding for trials on natural substances, unless it is patented and has gone to become a drug, it's going to be difficult to seek funding for reasonable trials, especially at later phases.

I think I'll stop at that. It's not possible to tell you everything about anti-angiogenesis and to cover what its agents are. But I want to give you the landscape, and I think that's what Henry asked me to do. I tried to give you some references for those of you who are interested in following up with that.

Thank you.

MR. DREHER: Thank you. Thank you. Okay. We're going to take some questions. I just want to say that I think it's a testimony to the breadth and scope of Dr. Chang's knowledge that I cannot think of anyone who could have done that presentation with such breadth and such scope and such fine details. I'm really happy I asked Ray to do this talk. It's really a beautifully exhaustive and complete and thorough talk.

I want to take some questions. Dr. Brewer, do you want to come up, in case people have questions for you? Yes?

PARTICIPANT: I'm a primary care physician with a complementary medicine practice. I'm often asked, what's the most reasonable thing that I could do as a patient to --

MR. DREHER: Simplified way to create a regimen that combines some of these natural therapies in a common sense way for anti-angiogenesis.

DR. CHANG: Of course. There are very simple things that can be done. Vitamin E, for example. I use that too, but also because it has so many other benefits.

PARTICIPANT: What dose do you use?

DR. CHANG: For me? Okay. 400 twice a day. I mix with --

PARTICIPANT: What else do you use --

DR. CHANG: But there are simple things that you can do. Vitamin D-3 is one of the least appreciated, and yet the cheapest and least appreciated thing around. Vitamin D-3 is 1,25-dihydroxycholecalciferol. It is not regular Vitamin D, which is D-1, which is what is in the milk.

We've done so many patients for those of, you know, my practice. We've checked their blood levels, and almost nobody walks in the office and has a high level of D-3. It's generally missing and it is, I think a vitamin that everybody -- almost everybody can take. Going beyond --

PARTICIPANT: What dose?

MR. CHANG: Dosage really has to be more tailored because that can be toxic. Vitamin D can be toxic. We use very high dosages. Thousands of units. You realize your multiple vitamins are 25 units or 50 international units. But that is not the right dose. Nor is it the Vitamin D that's in your regular multi-vitamin.

But most of the times, if you give 1,000 units, I haven't seen anybody going toxic with that. But it is very under-appreciated. Anything beyond that really depends on the case. What are we trying to prevent? What is the risk? Is there a family history of breast cancer, colon cancer? Is there a brachygene (?) involved? I mean, it depends. It depends on the patient. How much are they willing to do? How many pills do they want to take? How many cups of green tea?

So it's no one answer. I think it really has to be tailored, as I think all treatments should be, you know, pretty much tailored to the patient.

MR. DREHER: Yes? I think you had your hand up first. I don't know.

PARTICIPANT: Are there things you cannot combine tetrathiomolybdate with?

MR. DREHER: Question for Dr. Brewer. Are there certain things you cannot combine tetrathiomolybdate with?

DR. BREWER: We're just beginning to look at combinations. Theoretically, there is no limit on what we could combine it with. We've done animal work with radiation and it works very nicely. We're just starting to do work with combinations with chemotherapy.

There are no theoretical reasons why, first of all, anti-angiogenic therapy can't be combined with something else, or why copper-lowering therapy can't be combined with something else. The only thing is that the side effect of overtreatment is bone marrow reduction, and that is, of course, the side effect of a lot of other drugs, like chemotherapy.

The bone marrow suppression of copper-lowering is very benign because it recovers very quickly if you just back off on the dose.

MR. DREHER: A quick comment in answering your question. A lot of patients that I know are combining tetrathiomolybdate with Celebrex, and also with low-dose chemotherapy as a combined anti-angiogenic strategy. Some of those patients are also using some of the natural agents that Dr. Chang talked about: Vitamin E, omega-3 fatty acids.

I'm seeing more and more patients who are putting the pieces together and, at least anecdotally, it does not seem to be worrisome. There is a Web site, by the way, that is devoted to this issue, which you might be interested in. It's [www.cancerprotocol.com](http://www.cancerprotocol.com). It talks about tetrathiomolybdate and Cox-2 inhibitors and low-dose chemotherapy. It was set up by a man who helped his wife, who was a patient recovering from ovarian cancer. But it's a very, very good site. Yes?

PARTICIPANT: I have two questions. One is on the anti-angiogenesis inhibitors in general. And like a good example is Vitamin D-3, which you talked about. And I was wondering whether any of the others on your list are also immuno-suppressive? The second question is, just as in nature, you might

see anti-angiogenic substances, are there substances in nature which we could avoid which promote angiogenesis?

MR. DREHER: Two very good questions. The first question is, is there any sense that any of these natural anti-angiogenic compounds or nutrients may be immuno-suppressants? The second question is, in addition to using natural agents to try to suppress angiogenesis, are there any -- in nature, are there any promoters of angiogenesis that we should be avoiding? Did you want to comment on that?

DR. CHANG: I don't know if Dr. Brewer has noticed any significant reductions in lymphocyte counts. But certainly, neutropenia has been seen. I mean, I have seen tetrathiomolybdate causing it in patients who are post-bone marrow transplant -- patients with failed bone marrow transplants on tetrathiomolybdate develop, you know, even with a CP level of about 8, very low white counts that we needed to treat with.

We didn't want to stop, advise stop taking tetrathiomolybdate, because that may mean that we are letting the brake off, but that we treated with nupatin (?), a GCSF to stimulate. But yes, I mean, there is reduced growth. And if it affects the effector cells of the immune system, which turn around quickly. They are participating and they need to grow too; lymphocytes and neutrophils and theoretically, if you are anti-angiogenic to that extent. But a lot of the immune stimulants are anti-angiogenics.

Also, interferon is a very potent immune stimulant that is also a potent anti-angiogenic. So you really need to look at the individual items. As I mentioned, there is a Chinese herb that is a known immune suppressant. It is used to treat rheumatoid arthritis. So it depends really on the agent.

DR. BREWER: Can I make one other comment? Actually, we have not seen any problem with infection. The suppression is on the neutrophils, if it occurs. We haven't seen any effect on lymphocytes. Now we're doing a study in animals looking at the effect of copper reduction on infection. So far we've seen no effect. So it's very encouraging.

PARTICIPANT: How low does the white count go?

DR. BREWER: Well, the white count -- you know, you can get -- if you have pretty strong copper deficiency, you can suppress it just about as far as you want. We've seen them down around 1500 or so total -- the white count.

MR. DREHER: I'd like to also add -- then I want to ask you a second question -- that things like Vitamin E, green tea, omega-3 fatty acids, fish oil, are all generally immune-enhancing. So certainly, there's no conflict with quite a number -- green tea -- quite a number of the agents that are generally immune-enhancing. That's a generic term. But there's no immuno-suppression, certainly, with those agents. Excuse me?

PARTICIPANT: How about B-3 as an --

MR. DREHER: Did either of you have a comment on -- are there promoters of angiogenesis that we should be avoiding? Copper, obviously.

DR. BREWER: I'm not sure copper. You know, like in Wilson's disease, where it's very high, that it actually does anything bad, in terms of angiogenesis. We know it does in the eye if you put it in the cornea, but I haven't seen any evidence in Wilson's disease, for example, that it does anything bad. I'm not aware of pro-angiogenic substances in the diet. Are you?

DR. CHANG: I am concerned about niacin, for example. Anything that promotes blood supply, vascularization, and endothelial cell proliferation, and improves the micro-circulation. There are not enough studies, but there is mention, I believe -- there is summary mention, if you take a look.

I do counsel patients to avoid B-3, which is niacin and niacinamide. It can do that. I also do not like to see patients on ginkgo for promoting -- because it does improve circulation. But things that enhance blood flow. In Chinese herbs, there are a lot of things. Because it's well-known, actually, enhancing blood flow is one strategy of treatment, if you know traditional Chinese medicine. It's one major way of dealing with certain conditions -- it's to try to enhance blood supply. It may be a problem. So there are some things which may be of concern.

PARTICIPANT: What about capsicum?

MR. DREHER: Capsicum?

DR. CHANG: Not specifically, that I'm aware of.

MR. DREHER: Yes?

PARTICIPANT: -----

MR. DREHER: So the concern is whether Omega-6, which can be tumor promoting fatty acids -- do they have a role in angiogenesis as well? Do we know about omega-6 action?

DR. CHANG: Yes, I just mentioned. Actually, the study is on gamma-linoleic acid (GLA) as it inhibits angiogenesis. But you're right, I always counsel people -- I think the omega-3s are generally more benign, safer. In nature, as we know in TCM, there is a matter of balance, the yin-yang, the 3s and 6s are usually in balance. The 3s are more helpful for cancer than the 6s. The 6s are more immune suppressant, for example. It's useful for inflammatory conditions.

But specifically, though, you have to look at the fatty acids individually. For GLA, for example, there is good data that it is anti-angiogenic and it's useful for cancer in some cases.

MR. DREHER: Yes? You asked about how much copper to take, and I think the answer -- or you asked about how much copper or how much tetrathiomolybdate?

PARTICIPANT: No, I'm just asking about copper and in what food do you get it.

MR. DREHER: Okay. The idea here would be, I think, to avoid copper. So is it important -- that's right -- to avoid copper in food?

DR. BREWER: It's not really practical. The American diet contains about 1 mg of copper per day, which is about 25 percent more than we need. The only foods that contain a lot of copper are liver and shellfish.

Other foods which have sort of gotten a bad knock, like chocolate, nuts, legumes, and things like that, really don't have that much copper in them in comparison to other foods. I've measured them all. I think the tables in the old textbooks are wrong.

So if one wanted to keep your copper sort of on the low side, I would just avoid much liver and shellfish.

MR. DREHER: Yes?

DR. CHANG: I have a comment.

MR. DREHER: Oh, sorry. Yes.

DR. CHANG: Just one further comment. Again, I hope Dr. Brewer will give some insight into this. We have two patients that I recall trying to get the copper down that we were not successful using trientine and other methods, et cetera.

I think the problem -- in one patient, we traced it actually to the tamoxifen. Every time the patient goes on tamoxifen, the copper goes way up. The patient is very proactive and called the drug company. The drug company actually, I think, I believe it's Astra-Seneca (?), said that yes, there is data that Nolvadex increases copper. So that's one.

The other one, I have a hard time. I had one head and neck patient who tried desperately to lower his copper and tried desperately to get into a trial also. He was on anthro-feeding. We cannot get the copper -- the copper is very high, we cannot lower it. I checked with a nutritionist.

I checked with actually Mary Beth Augustine, who is giving a presentation down the hall, who is a New York City-based nutritionist. I called the various manufacturers of the anthro-feeding material. Very high copper in everybody's formulation. Nobody has a low copper feed that I'm aware of.

So there are things like that which add to the situation, which it may not have helped patient. But we couldn't get the copper --

MR. DREHER: Well, we'll come to that in one second. I'll come back to that item.

PARTICIPANT: What is the item with all of that copper?

MR. DREHER: Tube feeding.

DR. BREWER: Okay. With respect to the tamoxifen, what's really happening is that those kinds of hormonal-like treatments elevate the ceruloplasmin. So you're getting that kind of response, and so it becomes difficult. You have sort of an artificial elevation -- stimulus that elevates the CP, the CP does not become as good a reflector of -- and it dominates serum copper. So I think that's the explanation.

You're probably really lowering copper in a tamoxifen patient. It just doesn't look like it. The second thing about tube feedings is that our dieticians at the Clinic Research Center at Michigan have developed tube feeding formulae which give a relatively normal physiological amount of copper. So if anybody wants to contact our CRC, we can provide that information.

MR. DREHER: I just want to validate that. I had a brain tumor patient who was taking tamoxifen. Tamoxifen is also used for certain types of brain tumors. I had the exact same problem and the exact same scenario. They ended up -- Dr. Block was treating this patient. They ended up calling the drug companies, and found out, in fact, tamoxifen can keep the copper levels or the ceruloplasmin --

DR. CHANG: There is no better way to measure it --

PARTICIPANT: -----

MR. DREHER: The question is -- you're not going to know with that patient. You're just not going to know.

DR. BREWER: You can measure what we call free copper, which is to measure the total serum copper, and the ceruloplasmin, and subtract the two. If those two measurements are done pretty accurately, then you can show that the free copper is down, is lower than normal. So that's another way to do it.

MR. DREHER: I'm sorry, what was your chemotherapy question, ma'am. I apologize.

PARTICIPANT: Oh, whether it lowers your immunity and -----

MR. DREHER: Does chemotherapy lower immunity? I think I can answer that. Yes, it does. Can it give you secondary cancer? Yes, it can in some cases. In some types of chemotherapy. Yes?

PARTICIPANT: -----

MR. DREHER: The question should perhaps be, would it be useful to avoid foods with niacin? I'm not so sure about that. I would think it would be useful to avoid supplementation with niacin.

DR. CHANG: Yes, that's all.

MR. DREHER: D-3?

DR. CHANG: D-3 is not in foods. D-3 is made from D-2 after you get exposed to sunlight. It is made in the skin. But most of us don't get enough sunlight. This is actually very interesting, just to digress. The body is very smart over time, or God is very smart over time in pushing us through evolution, that there is an intrinsic mechanism in the skin for protecting against cancer, which is D-3.

The sun induces D-3. The sun also induces cancer, or puts you at risk. So it's sort of a balancing thing. But D-3 is made -- you have to take D-3 as a supplement. It's not in foods that I'm aware of.

MR. DREHER: I want to make a quick comment and let Dr. Chang comment on this. I'm aware of literature that suggests that Vitamin E succinate is the type of Vitamin E that has the most potent anti-angiogenic activity in in vitro and in animal studies. so I would think that if you're looking to use Vitamin E -- Ray, you may disagree -- if you're looking to use Vitamin E as an anti-angiogenic, you might want to go with Vitamin E succinate. You want to comment?

DR. CHANG: Yeah, I saw that. I don't think so. Because there is only one listing, in one piece of literature, from one lab. Things are not generally proven that way.

Again, because I think this in vitro testing, the models are sometimes not reproducible, et cetera. It is -- I don't think we can just put that much weight on that one study. Even the whole thing about Vitamin E. If I have to rank things about how much data is there for a certain item being anti-angiogenic, Vitamin E is a little shaky. It's not that much.

But Vitamin E, I take again, because of many, many other healthful benefits, et cetera, and in the sense of the very excellent -- you know, the benefit to risk ratio, it's quite safe. But I won't rely on Vitamin E as an anti-angiogenic.

MR. DREHER: Yes? You've been --

PARTICIPANT: I just have a brief question. What about coffee? You didn't mention it. Is that going to --

DR. CHANG: No, I don't have a problem with it.

MR. DREHER: No problems with coffee? No problems with coffee. Okay. Yes?

PARTICIPANT: Any research on -----

MR. DREHER: Yes, Celebrex and Viox (?) are both Cox-2 inhibitors. The question is, are they both considered to have anti-angiogenic properties. I think most of the research on colonic polyps, preventing colon cancer, has been done with Celebrex rather than Viox. But I'll let Dr. Chang.

DR. CHANG: There are a lot of studies on Cox-2 inhibitors and cancer. A majority of the studies with drugs are done with Celebrex and not Viox.

There is also a study comparing Viox and Celebrex showing that the side effect profile is better with Celebrex at that high dose. It's a high dose. It's not your regular dose. It's much higher. so there is difference in side effects.

Most of the research is based from Celebrex, although Viox may work. There is a third -- for those of you who are interested -- Cox-2, which is available in this country. It's Mobec (?). But there's very little research on that.

MR. DREHER: I just want to add that Dr. Andrew Dannenberg at New York Hospital-Cornell Weill (?) had done research showing that resveritrol and curcumen and Bprophilus (?) and green tea are all -- and rosemary are all extremely potent Cox-2 inhibitors, natural Cox-2 inhibitors, that probably and apparently also have anti-angiogenic properties.

Yes. You've been waiting there for awhile.

PARTICIPANT: What's the most recent data on Cox-2 --

MR. DREHER: What's the most what?

PARTICIPANT: The most mature data?

MR. DREHER: What's the most mature data on Cox-2 inhibition and breast cancer? There is an amazing paper by Dannenberg and his team that was just published within the last couple of months in -- I forget the journal. But if you look up Dannenberg and combine it with Cox-2 on Pubnet, it is the single best review that has ever been written.

The in vitro and in vivo pre-clinical work is very impressive. I can't comment on whether there is any real clinical work. But I'll let Dr. Chang.

PARTICIPANT: Will you spell Dannenberg for us?

MR. DREHER: D-a-n-n-e-n-b-e-r-g. Superb research. He's a professor of medicine at Weill-Cornell, a chaired professor.

DR. CHANG: Again, referring to the same studies. But 6 months ago, in the presentations from ASCO, American Society of Clinical Oncology, the detail on all Cox-2 inhibitors and breast cancer was

presented. There is, Number One, Cox-2 receptors on breast cancer cells in vitro. Number Two, it prevents tumor regeneration -- the initiation of tumor. In established tumors, it prevents its progression and growth.

There is currently planned trials carried at -- or planned trials at Sloan-Kettering, for example.

PARTICIPANT: -----

DR. CHANG: I don't have an exact percentage number. I think in the order of 75-80 percent. But don't quote me on that. I think you should refer back to the Dannenberg studies.

MR. DREHER: A lot of solid tumors overexpress Cox-2. Yes?

PARTICIPANT: When you speak about -----

MR. DREHER: To cockrels? All right. When you were talking about Vitamin E as an anti-angiogenic, were you talking about alpha, beta, gamma, or any form of Vitamin E?

DR. CHANG: An E succinate was sub-studied. But I don't think -- again for many of you who don't know there are many kinds of Vitamin E. There's also ----- which are not even tocopherols. They are Vitamin Es also. So it's a broad family.

But I wouldn't be surprised if in one form, there's activity that the other forms will have some activity. I don't think that it's all different. But the study is only of one form.

PARTICIPANT: -----

MR. DREHER: Yes, okay. Colon cancer that is in remission? How effective might tetrathiomolybdate and Celebrex be in a colon cancer patient in remission in the hopes of warding off a recurrence of the disease?

DR. BREWER: Well, I predict that it will be very effective. But we don't have the data to back it up. But I believe that relatively minor disease, and we are beginning to get some data on mesodibyoma (?), which is a very, very bad tumor. But you can de-bulk it for the most part.

So far we're having pretty good success with Dr. Harvey Katz at Wayne State at preventing recurrence. It's very, very early in the study. But I believe that when the disease is kind of minimal, angiogenesis inhibition is much more effective. The model was the HER-2/neu mouse that I showed you. I think we can keep those tumors from ever appearing. But the data are not in on the question you asked.

MR. DREHER: I think we should take probably just about two more questions and then move on. You've been very patient.

PARTICIPANT: I work for six doctors. I get six different answers.

DR. DREHER: She works for six different doctors and gets six different answers.

DR. BREWER: Why only six?

PARTICIPANT: During chemotherapy, 48 hours pre- and post-, do you advise me to take E, Vitamin D-3 or no? Is it enhancing the chemotherapy too much or not?

MR. DREHER: The question is, is there a problem with taking certain vitamins, particularly E and niacin?

PARTICIPANT: No, E and D-3 during --

MR. DREHER: D-3 during chemotherapy. I don't know if it has any relevance to the issue of angiogenesis per se, but there is an ongoing debate about whether the anti-oxidants offset the action of certain chemotherapies. We're having a whole session on that. Dr. Persad will address that. I want to get someone who has hasn't asked a question. You, sir.

PARTICIPANT: Captopril is a very known, very well known anti-cancer drug. In the last about 5 years or so -----

MR. DREHER: Okay. There was a drug called Captopril which was apparently exciting about 5 years ago, and there was a recognition at that point that it had anti-angiogenic properties, and it seems to have fallen off. What's going on with Captopril? Do you know about this, Dr. Chang?

DR. CHANG: There are a lot of drugs. I mean, again, this is not a session on drugs and -- off-label use of drugs for anti-angiogenesis, which could be a whole different session. There are a lot of drugs, and certainly Captopril is one of those drugs. We have never used Captopril because there are drugs with a better safety profile, et cetera.

You know, if you don't have hypertension, and if you don't have the heart to, you know, to push a dose of something like Captopril and run the risk of hypotension, et cetera. But there are other drugs -- doxycycline, the tetracyclines, studied at the University of Indiana -- that are very well documented anti-angiogenics.

There are certain antibiotics that are very well documented anti-angiogenics. Chromium sodium -- there is research done in England showing it's a useful anti-angiogenic. Except that's only -- but that doesn't get absorbed very easily. The liver doesn't -- so you can only use it as an inhaler. Orally, it doesn't -- you know, absorption is erratic. so there are all these issues.

But you have to take, if you're using a drug, you have to use -- heparin, as I said, is useful. But how often would I put somebody on heparin in order to do anti-angiogenesis unless it's a trial? Because you run all these side effect risks. You really -- I mean, in the treatment of any patient, you know, the first thing is to do no harm.

At least you put together a regimen that is the least harm that is appropriate to the problem at hand. You know, if it's prevention, you absolutely should do no harm. I mean, I wouldn't unless it was very high risk -- I would not consider using a drug with side effects. So that is the issue. I think that's why it sort of didn't get more studied.

MR. DREHER: Does everybody want to stay a another couple of minutes and take a couple more questions?

PARTICIPANTS: Yes.

MR. DREHER: Okay. I think we have about a -- we're going to take about three more questions because we've run quite over. I'm delighted with the response. You've been waiting, and then you -- Yes, I'm sorry.

PARTICIPANT: -----

MR. DREHER: I think Dr. Brewer would answer that green tea.

PARTICIPANT: Could you repeat the question?

MR. DREHER: The question was, of all of the anti-angiogenic compounds we have discussed today, which would be the single one that would be the most exciting and promising. It occurred to me that perhaps Dr. Brewer might say tetrathiomolybdate. Whereas, Dr. Chang may have a different view.

DR. CHANG: I agree. I think it's very exciting. That's why I think Henry asked us both to be here today. It's very exciting. Again, I think it's exciting because it works in this cocktail fashion.

It doesn't have one single mechanism of action and it's a broad-based approach. It's not very toxic and it's very exciting. But otherwise, I wouldn't isolate any particular.

Again, along with my general way of thinking, I think a cocktail approach is the best approach. Of course, Chinese medicine, herbal medicine, has been doing cocktail approaches for thousands of years.

MR. DREHER: Okay. Yes, you've been very patient.

PARTICIPANT: -----

MR. DREHER: Actually, we're going to have to -- you were asking about the angiogenic effect of what? I didn't hear you.

PARTICIPANT: -----

MR. DREHER: Human Growth Hormone. Are there are angiogenic effects of Human Growth Hormone and should that be a concern? If Dr. Chang doesn't know, I can tell you I don't know. We don't know the answer. I will make -- yes. You were very patient also.

PARTICIPANT: Are any of these anti-angiogenics going to have a significant effect in later treatment?

MR. DREHER: Dr. Brewer began to address that issue. I think he should answer that.

DR. BREWER: Well, in our experience, it looks like we -- in many cancers that are well-developed -- we can kind of halt progression for awhile. But then we lose it. In the case of that dog osteo-sarcoma, that one actually shrank and we had evidence that it was necrosing a little bit. I think that's because the blood vessels remodel in some of these tumors. That is, you get rid of old ones and grow new ones. If you're stopping the growth of new ones, then the tumor is going to shrink.

So I think that in well-developed cancer, there is some room for this kind of therapy. But I don't think it's going to be nearly as successful as in early cancer, where the disease is small.

MR. DREHER: I think it might be seen as a bridge. A lot of patients with widespread metastatic disease see it as a bridge. Something to buy some amount of time because it can, conceivably, slow progression. Yes.

DR. CHANG: I'd like to ask Dr. Brewer a question. Dr. Brewer, what happened to patients who were stable in your Phase I study?

DR. BREWER: Five of them still are on the study, including the lady who is out now 3-1/2 years. The breast cancer patient did have progression at one site. The way these protocols work, once they have progression at one site, they go off the therapy. So you know, for the practice of good medicine, I would like to have nipped away at that one and then continue her, but she was off.

DR. CHANG: Colon, metastatic colon?

DR. BREWER: I think it was a renal cell, is that what you're -- we don't have any with metastatic colon cancer still on study.

MR. DREHER: I want to get to the people who we haven't heard from. Yes?

PARTICIPANT: What about bind weed?

MR. DREHER: Does anyone know about bind weed? You have stumped us all. Yes?

PARTICIPANT: Since niacin was implicated as an angiogenic, are other statin drugs -----

MR. DREHER: Yes. There is a lot of interest in statin drugs, and the expert in this area is Dr. Chang.

DR. CHANG: Niacin is used -- it's Vitamin B-3. It is used to lower cholesterol. It is a very old treatment. Statins are a wholly different class of drugs. That's HMG-coA reductase inhibitors. They are used to lower -- very effectively -- lower blood cholesterol. They are actually useful as anti-cancer agents. So that has nothing to do with angiogenesis. They are totally different things.

For those of you who are interested to read a little bit more about niacin and the concern, there is a nice section in John Boik's book on natural agents and cancer on niacin.

MR. DREHER: Yes. I want to recommend that book. John Boik has done an amazing job. He wrote a book called "Natural Compounds in Cancer Therapy." You can find it online at Oregon Medical Press. He talks about all these issues. John Boik, B-o-i-k. The actual name of the book is "Natural Compounds in Cancer Therapy."

PARTICIPANT: They have it downstairs.

MR. DREHER: They have it downstairs. Yes, you've been waiting.

PARTICIPANT: -----

MR. DREHER: I'll repeat the comment. Human Growth Hormone can increase Insulin Growth Factor 1, and there's a great deal of concern right now about high levels of Insulin Growth Factor being associated with cancer progression. So people should be very careful about Human Growth Hormone. Yes?

PARTICIPANT: -----

MR. DREHER: Does anyone know about a curcumin study promoting what --

PARTICIPANT: Lymphoma.

MR. DREHER: Promoting lymphoma cell growth? That's -- I've never heard of that. That's interesting. Because curcumin has been found in just about every pre-clinical study to have anti-cancer properties of all kinds. So that surprises me. It should be something to looked into and found out, particularly for lymphoma patients. Yes?

PARTICIPANT: -----

MR. DREHER: Good question. The comment is that John Boik, in his book, tries to calculate reasonable dosages based on pre-clinical research for what kind of dosages people should take in these natural compounds. The question for Dr. Chang -- does he think that that's a reasonable -- does he think that those are reasonable calculations?

DR. CHANG: No. I generally don't believe in extrapolation too much. I would not extrapolate those from animals to humans, although a lot of times you need to do that. No, there is sometimes clinical data.

There are certain things we're limited by the dosage we can give because of side effects. You can administer a lot of curcumin or have patients eat a lot of curry, but it's going to upset their stomach. It has to stop -- rats cannot complain. So I don't like to extrapolate.

MR. DREHER: I think I've had that -- Oh, Dr. Brewer.

DR. BREWER: I agree.

MR. DREHER: Dr. Brewer agrees.

On that note, I'm going to thank you all for coming because you're a wonderful audience. Thank you very much.

(Whereupon, the PROCEEDINGS were adjourned.)

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