

Comprehensive Cancer Care: Integrating Complementary & Alternative Therapies  
New Biological Therapies

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Dr. Kronenberg: We'll have each presenter talk for about 20 minutes. If there are one or two burning questions immediately after their presentation, we'll take them. At the end our commentator will speak and then we'll open the floor to questions from you. You're welcome to speak from the microphone. If you choose not to do so you're welcome to hand in a question to us, and we'll proceed that way.

No biography for myself or Dr. Simone was in the program. I am a physiologist by training and currently am director of a comprehensive and alternative medicine program at Columbia University. We're one of ten centers of alternative medicine funded by the National Institutes of Health, the specialty centers. Our focus is on women's health. We're just beginning to develop projects right now in the area of breast cancer. We're particularly interested in traditional medicines and botanicals.

Our first speaker will be Dr. Bakács, who had his training in immunology, his PhD and MD, in Hungary. He then spent time in Stockholm at the Karolinska Institute in the 1970's looking at cytotoxic lymphocytes. He spent time in Manchester, and more recently has been at the NIH National Cancer Institute looking at bispecific antibodies in the treatment of cancer. He is the scientific director of the United Cancer Research Institute in Virginia. The Institute is headed by Dr. Csatory, who will not be here this morning because he is ill. Dr. Bakács will be doing Dr. Csatory's presentation as well, after he does his own. The title of Dr. Bakács'

presentation this morning is “A Preliminary Report of Controlled Trials of Virus Vaccine for the Treatment of Acute Hepatitis B and C.” Dr. Bakács.

Dr. Bakács: Yesterday, you might have heard the lecture of Professor Freeman, who introduced the use of avian viruses in the treatment of cancer. Today I am going to talk about another possible use of avian viruses to treat infections, specifically hepatitis B and C infection.

This is a controlled study on hepatitis B and C patients which has been recently published in *Anticancer Research*. Viral hepatitis is one of the most common infectious diseases of humans. It is probably caused by at least six different viruses. It is well known that viral hepatitis is initiated by a specific antiviral cellular immune response. However, the damage to the liver is caused by a cascade of non-specific effector systems. Five to ten percent of acute hepatitis B infection, but up to 85% of HCV infections, progress into chronic active hepatitis in which the liver cells are gradually destroyed.

It is also well established that chronic hepatitis B and C is responsible for liver cirrhosis and various malignancies including hepatocellular carcinoma. It is estimated that by year 2000 the number of HBV carriers will be 400 million all over the world, and the number of HCV carriers is well over 100 million. The problem of viral hepatitis is of global proportions. It is not surprising that the primary hepatocellular carcinoma ranks among the ten most important cancers of the world. Hepatitis B prevention is already solved and introduced into 70 countries around the world. Unfortunately HCV prevention is not yet solved. Until the full effect of these programs is felt, the treatment of acute hepatitis B and C is still a problem.

Once an acute infection starts, it is very difficult to prevent the progression of the disease into chronic infection. It was Dr. Csatory's idea that avian viruses, which are apathogenic to

humans, could be used to prevent other viral diseases like hepatitis. The virus he used was the avian Bursal Disease Virus (BDV), which is an infectious disease in chickens. It's a double-stranded RNA virus from the Birnaviridae family. You've heard about the model on mammals and monkeys which were infected by human hepatitis A virus. The monkeys were successfully cured by the Bursal virus. In treating cancer patients with this virus, occasionally he observed a rapid resolution of viral hepatitis. It is very important that the Bursal Disease Virus is apathogenic to humans, and therefore has no public danger.

In this study we included 84 patients of both sexes, 43 patients from B and 41 patients from C hepatitis. The patients were randomly divided into two groups. One was treated by conventional treatment, whereas the other group was treated by the virus. The reason for hospitalization was jaundice and other typical signs of acute hepatitis like fever, severe malaise, loss of appetite and a 10 to 100 fold elevation of alanine-aminotransferase (ALT) level. I don't want to go through details, but the exclusion criteria from the studies were according to international standards.

The treatment was an intranasal treatment. It was live, attenuated virus produced by the Phylaxia-Sanofi company in Hungary. The treatment consisted of 4,000 units of virus, once every day for the first week, then three times a week for two weeks, and then once a month for six months.

We established four groups of patients – remission, relapse, late remission, and chronic course. These are all according to internationally established rules. The statistical analysis was performed by the Yates correction of the chi-square test. This shows a typical response of two patients. The first one is treated by the virus; the second one is treated conventionally. This is the aminotransferase level, from the start of the treatment. Its decrease is shown as the weeks

pass. By the third week of treatment, the vaccine treated patient recovered, and the level was in the normal range. The same with conventional treatment took five to six weeks.

This is a summary of the results of the study. Perhaps the most important result is that the progression to chronic active hepatitis was prevented in the vaccine treated group with B hepatitis. Thirteen percent of patients progressed into chronic hepatitis in the control group. The same is 9% and 26% for the C hepatitis. The relapse rate was also significantly different in the two groups. It was 5% for the hepatitis B patients in the vaccine treated group and almost double in the control group. There was an even bigger difference in hepatitis C – 32% in the vaccine-treated group, and more than twice that, 79% in the control group.

Late remission, which is remission over six months, was also different. No late remission was in the hepatitis B vaccine treated group, whereas it was 17% in the control. The same for hepatitis C was 14% and 42%, again more than double. Perhaps it is also a good sign of the effect of the vaccine that for fast remission, within one month, 50% of the patients in the vaccine-treated group went into remission within a month, whereas only 26% of the patients in the control group did so. In hepatitis C, 50% of the patients in the vaccine group went into remission within a month, compared to 21% in the control group. The duration of the disease was very much shortened in both groups. In the B group, it was shortened from 7.5 weeks in the control to less than 6 weeks in vaccine treated patients. In the C group the duration of the disease was decreased from almost nine weeks to somewhat more than five weeks.

It is very important to say that there is no side effect of this treatment. We don't know the mechanism of action in patients, but there are very good animal models. One was published by Guidotti and coworkers in the PNAS some two years ago. This was a transgenic mouse model of hepatitis B virus infection. The study showed that hepatitis B gene expression and

replication can be abolished by a noncytopathic, cytokine-dependent pathway. This occurs first of all by the induction of TNF-alpha and interferon alpha and beta, which is produced intrahepatically by the intrahepatic macrophages. In that model, it was the lymphocytic choriomeningitis virus (LCMV) which induced this lymphokine secretion and resulted eventually in the cure of the hepatitis B infection.

We believe that this might be also an explanation for the results we see in patients, but also there are several other possibilities. There are reports when hepatitis B infection was resolved after an intermittent infection by hepatitis A or C. We concluded that the Bursal Disease Virus vaccine – which is called MTH-68/B – therapy is safe and efficient to treat hepatitis B and C infections. We believe this is important to prevent chronic infection and to prevent hepatocellular carcinoma. To confirm results, of course, we will need further studies.

Finally, I would like to show three cases of chronic hepatitis patients. This was three women. We followed the patients from two to twelve years. One had hepatitis C and two had hepatitis B infection. Before the vaccine therapy, all the patients were in very bad condition. They couldn't get out of bed. One of them was moribund. All of them had decompensated liver disease, so there was no chance of interferon treatment. These patients were treated by massive dose of this vaccine. One of the patients received 900,000 units of vaccine, which meant that throughout four years she got the vaccine treatment.

The clinical symptoms and also the biochemical abnormalities were resolved in two patients, and these two patients recovered fully. One of them is negative by the polymerase chain reaction (PCR) test. The other one is still positive, but has practically no complaints. The third one, the moribund patient, is able to do light work and is leading a normal life. We don't

know of any record of cases of such serious chronic hepatitis which went into long-lasting remission.

Finally, let me show you patients. Here again are the alanine-aminotransferase levels. The follow-up is not in weeks but in months. This patient was followed more than 40 months. The arrow indicates the start of the treatment. This patient recovered fully biochemically, which is very important. Throughout the follow-up period the cholinesterase level is increasing. The increasing cholinesterase level shows the recovery of the liver cells. Even after several years of chronic infection and very serious clinical condition, the liver can regenerate provided the virus infection is stopped.

The second patient was the most serious case. As you see, for a while the biochemical changes were slight. Eventually they almost reached the normal level, which is 40. Surprisingly, even she, who had large liver and large spleen, experienced liver regeneration. You see the cholinesterase values are starting to increase. This is already in the normal range. Thank you.

Dr. Kronenberg: Are there any questions people want to ask at this point?

Participant: Is the vaccine available?

Dr. Bakács: Not yet. It's an experimental treatment. We are working on that.

Participant: Why did you select the chicken virus as the tool?

Dr. Bakács: The number one reason is that it is apathogenic to humans. The rest was trial and error method. Dr. Csatory's principle was that when using a virus it should be apathogenic to humans. Because the Bursal Disease Virus is known to be apathogenic to humans, this was the first reason of choice.

Participant: (Did not use microphone.)

Dr. Bakács: Not this one. The Newcastle Disease Virus. In the next lecture I will talk about Newcastle Disease Virus. That is also an avian virus.

Participant: Yesterday there was a presentation about the Newcastle virus being used to shrink brain tumors in children. Do you think there is any significant similarity, or is it a very different pathway in effect? What's going on here that's similar, that these avian viruses can do both these things?

Dr. Bakács: My simple answer is I have absolutely no idea. In hepatitis, there are several mouse models. The one I mentioned gives a very good estimation of what can go on in patients. This is more or less virus interference. What goes in cancer patients, I will talk about in the next lecture. It's a different business.

Dr. Kronenberg: Dr. Csatory is ill today and unable to be with us. Dr. Bakács graciously agreed to present his work as well. Dr. Csatory had his medical degree in Budapest, Hungary, and is also licensed in the United States. He was the first to use avian viruses in the treatment of

cancer. That was first published in 1971 in *The Lancet*. Today he heads the United Cancer Research Institute in Virginia, for which Dr. Bakács is the scientific director. The presentation that Dr. Bakács will make now for Dr. Csatory is on the successful use in patients with advanced cancer of the Newcastle Disease virus vaccine.

Dr. Bakács for Dr. Csatory: To make it clear, this is also an avian virus, but not the one which I talked about before. This is the Newcastle Disease Virus, which you heard about yesterday in the treatment of glioblastoma patients. This treatment of cancer is not new. It has been known from the beginning of the 20<sup>th</sup> century that viruses exert oncolytic effect on malignant cells. Fifty-three viruses have been tested as anticancer agents, and thirty-eight were found to have antineoplastic effects. Unfortunately, most of the oncolytic viruses are also neurotropic and have other human pathogenic effects. It is a further danger that introducing live viruses into the environment has public health consequences. Massive doses of viruses are required to treat cancer patients, so an ideal viral candidate should be oncolytic but if possible apathogenic to humans. The list of such viruses is very short. Fortunately it includes the Newcastle Disease Virus (NDV).

The idea to use avian viruses to treat cancer comes from Dr. Csatory. He treated his first patient with this virus exactly 30 years ago. The first results of this treatment were published in *Lancet*. He showed that very advanced cancer patients went into complete remission, and this lasted over a year. In 1993, there was an open, phase II, placebo-controlled multicenter clinical trial using this vaccine. The patients who were included in this study were no longer responsive to conventional therapy. Regression and/or stabilization of tumors occurred in 55% of the cancer patients. This was published in *Cancer Detection and Prevention*.

The Newcastle Disease Virus is a large RNA virus. It belongs to the avian paramyxovirus group. It causes very serious epidemics of pneumoencephalitis in chickens. Fortunately, the virus is minimally pathogenic to humans. It is especially important that it is minimally neurotropic. We have used this virus to treat over 500 cancer patients without any serious toxicity. This virus is also produced by the Phylaxia-Sanofi company in Hungary. A vial contains  $10^{7.4}$  viral particles. The virus can be administered by inhalation and intravenously as well. The pharmaceutically effective amounts of vaccine range from one to four vials a day, or maybe it could be even more. Maintaining those after complete remission is four vials per week. This could be continued for years.

The mechanism of action is very poorly understood. We know from animal experiments that NDV is able to kill cancer cells directly and selectively. It was also shown that normal cell lines transfected by different oncogenes become 1000-fold more sensitive to NDV infection. We have preliminary experiments on a pheochromocytoma cell line, which express the Ha-Ras oncogene, that this cell line underwent apoptosis after NDV infection. The induction of apoptosis correlated with the expression of Ha-Ras oncogene.

To treat a patient you need a very large amount of virus for a long time. It is not surprising that there is significant antibody production to this virus. On this axis you can see the reciprocal antibody titer. This is a logarithmic scale. On this axis you see the viral dose, which is approximately equivalent to the length of time of the treatment. Each dot is a different patient. This was done in 30 cancer patients treated from two months up to eight years. You see there is a very huge induction of antibodies, which seems to decline as the time goes on. The question is whether the antibodies in the patient inhibit the therapy. We don't know. This should be studied further.

I will describe briefly four cases, four cancer patients, who all had very advanced cancer. They had exhausted all conventional therapy, practically were given up for conventional therapy. All of the patients responded to various degrees to NDV therapy. The purpose of this report is not to generalize about likely outcomes, but simply to demonstrate that the effect of this viral vaccine in some cases of advanced cancer is significant. I have all the detailed case histories of these patients with me. If anybody is interested in further details, I can present that.

Case one was stage IV recurrent rectal cancer. He was treated first by chemotherapy 5-FU. It was ineffective. Indeed, the DeVita textbook states that “Overall, 5-FU does not demonstrably affect survival for all patients treated; it is associated with a median survival time of six to eight months.” This patient lived longer than a year. These four months wouldn’t be too significant, except that this patient died in heart failure. When the autopsy was done, no tumor was found.

The second patient is a melanoma patient, grade III. He was diagnosed 14 years ago. The first melanoma was surgically removed. Then the patient went through chemotherapy, surgery, all conventional therapy. After the second melanoma recurrence, he started the NDV therapy. Ever since, he has been on the therapy. He is alive 14 years after the diagnosis. For grade III melanoma, according to the DeVita textbook, cure is not a realistic aim. The survival is six months.

What is perhaps even more important is that this patient interrupted the therapy twice, once in 1993 or 1994 for a year. The second recurrence occurred after one year without the NDV virus. When I prepared this slide about a month ago, the patient was symptom-free. Just after I left to come to the U.S. I got a surgical report that he had a third recurrence of melanoma, with lymph node metastasis. The patient stopped the treatment about 1.5 years ago. One of the

most important messages of this therapy is that you should use the virus in very high dose and for a long time. This patient has been on this treatment longer than 10 years.

The third patient is a non-Hodgkin's lymphoma patient who also survived his initial diagnosis by eight years. He first started conventional chemotherapy, but after the first cycle of chemotherapy he refused any further chemotherapy. Now he's only on the NDV treatment.

The fourth case is a widespread metastatic colorectal cancer patient who survived her disease by 27 months. She didn't receive NDV properly. She often interrupted the NDV treatment because of traveling, reduced the dose. Then unfortunately we lost her. We believe that if she had received the treatment in a more proper way she would have survived even longer.

There are dangers with viral therapy. Anybody who is introducing self-replicating "drugs" into the environment, even with therapeutic intent to a limited number of patients, requires ethical and medical review, as with any other live virus treatment. However, unlike many pathogenic virus vectors, such as herpes virus vectors, the avian NDV poses no public health danger to the general population. The attenuated NDV vaccine has been used in veterinary medicine for 50 years. No virus conversion and no other genetic variation was observed in its natural host.

We conclude that the use of attenuated viruses, avian viruses, which are essentially apathogenic in humans, represents a new and hopeful avenue in cancer treatment. MTH-68/H vaccine meets all the requirements of such a virus. Some individuals with advanced cancer appear to experience amelioration of their symptoms or regression, even complete regression, of their tumors. We know that randomized clinical trials are necessary to evaluate properly the efficiency and safety of this experimental therapy. But we believe that the presented cases are

educational, since they challenge the conventional medical wisdom that most cases of advanced metastatic carcinoma and others cannot be cured.

Finally, let me show you a table which is a summary of 21 similar cases, for all of which we have the detailed medical records. All had metastatic cancer. All were treated, after conventional therapy was futile, by the NDV. Most of them went into complete remission. In the last column you see the years in survival – from one year up to 16 years. This, and the placebo-controlled clinical trial in 1993, which was published, give us the belief that this virus has potential and is worth further attention. Thank you very much.

Dr. Kronenberg: We can take one or two questions if you have them. Certainly it's very interesting data. Some of these people who were in good remission dropped out. You didn't get into toxicity. I wondered about that, and also about expense.

Dr. Bakács: Could you repeat the question?

Dr. Kronenberg: The fact that some people who were doing very well dropped out and stopped taking them made me curious about toxicity, and also expense, the cost.

Dr. Bakács: This is again an experimental therapy, so we cannot give a price. The most serious side effect is a pink eye if the vaccine is directly dropped into the patient's eye. Usually all patients experience fever after the application of the virus, on the second day. However, this fever usually lasts only a day. Usually it's more a subfebril reaction than a real fever. There is no serious side effect to this treatment.

Participant: You showed 21 responses. Did you say you treated 500 patients, and would that mean your response rate is about 4%?

Dr. Bakács: No. These cases were the most spectacular cases. As to the response rates, we have a controlled study. In that (if you include complete remission, partial remission and stabilization of the tumor) the response rate was 55%. From the 500 patients, we are currently evaluating the data for about 300. That is just to say that the toxicity of the treatment is negligible.

Participant: (Did not use microphone.)

Dr. Bakács: I can look. I have the paper, so I can tell you. To my knowledge the complete remission was 8% in that study, but I have to look at that.

Participant: I have a quick question about why you're only using this for advanced cancer. What's the theory behind using it in advanced cancer versus using it as a first line treatment?

Dr. Bakács: My answer is very simple – because it is not allowed. This is an experimental therapy. The only way to get into this program is when the patient has exhausted every other possibility. It's that simple. You're absolutely right that this is not the right time to start the treatment. But we have no other option.

Participant: Are there any protocols going on in the United States?

Dr. Bakács: No. We would like that very much, but not yet.

Participant: So one has to go to Budapest to get the treatment done?

Dr. Bakács: Exactly. Yes.

Participant: I know that in Tijuana at the Hoxsey Clinic they were giving out MTH. Is that the same?

Dr. Bakács: I have no idea. From where?

Participant: At the Hoxsey Clinic in Tijuana. They were giving it as a nasal inhalant.

Dr. Bakács: This is new for me. We have a patent on this, so I am surprised.

Participant: You might speak to them.

Participant: There was some part of your data which indicated that stimulation of interferon and other cytokines might be part of the mechanism, at least in hepatitis. One might presume that to be in cancer. Do you have any data that suggests that there might be any specific

cell-mediated enhancement that's more related to the tissue type of the individual or the cancer that's involved?

Dr. Bakács: Here the mechanism is not cytokine induction, so not in cancer. It might have also a role, but we believe this is more of a direct lytic action of the virus. This virus replicates a thousand times faster in malignant cells. Also it induces lysis in nude mice, which have no T-cell reaction. We have shown in preliminary experiments that this virus induces apoptosis. We believe that this is an apoptosis and direct lytic effect. However, it is very well possible that the cytokine induction (and NDV is one of the best interferon inducers among all the viruses), has a role. No question about that.

Participant: Have you looked at any parameter of lymphocytic reaction against the tumors at all?

Dr. Bakács: No, not yet.

Dr. Kronenberg: Thank you very much. Our next speaker is Dr. Charles Simone, who is a medical oncologist, a radiation oncologist and a tumor immunologist. Dr. Simone received his medical training and masters of medical science at Rutgers. He has done some work on plant compounds called lectins and their cancer-killing properties. Dr. Simone is particularly interested in nutrition and cancer. He is the author of several books, on nutrition and cancer and on breast and prostate health. Since 1988 he is the director of the Simone Protective Cancer

Center. His presentation today will be on shark cartilage use in advanced cancer patients. Dr. Simone.

Dr. Simone: Thanks very much. We treated advanced cancers using cartilage and lifestyle changes. What was omitted on this slide was lifestyle changes. That's critical in what we'll be talking about. We know that one of every three people will develop cancer, and by the year 2000, two of every five will develop cancer. We're not getting anywhere very quickly. From 1930 to the present, there's been no progress in the treatment of adult cancers. A person who gets cancer today will live as long as a person who got it in 1930. Despite everything we've done – chemotherapy, viral therapy, you name it – we see no changes at all. We need to turn our attention to two areas: prevention, which I have devoted a lot of my time to in the last 15-18 years, and also the investigation of new types of substances.

In the 50's, Dr. John Prudden investigated the use of bovine cartilage in the treatment of cancer patients and other people. A surgeon, he first used this to look at its effects on wound healing. Then he looked at other patients with rheumatoid arthritis, osteoarthritis, skin allergies, psoriasis, ulcerative colitis, systemic sclerosis, and cancer. He reported on 33 patients in a fairly prestigious journal in 1985. He showed that 35% of those people had a complete response.

It's important to define these words. Cancer doctors always use jargon, and some words sound terrific. Complete response is the complete disappearance of a tumor, generally for at least four to six weeks. Twenty-six percent of these 31 people had a complete response, but with relapse. Nineteen percent had a partial response, less than 50% reduction in a short period of time. Ten percent of those had a relapse as well. The curiosity about this information is that there has been no follow-up study, no follow-up publication. These numbers represent a

fantastic response rate overall. A great many of these patients with very evil tumors had a major response. Yet we don't know of any follow-up information published by Dr. Prudden. I've talked to him about that many times, to publish the data. It has not come out.

What's in shark cartilage? We all have cartilage. We have some in our ears, the tip of our nose. What makes cartilage stiffer and not as fleshy is that it has certain enzymes and factors in it to inhibit the migration of blood vessels into that site. It also has certain enzyme activity, certain growth promoters. They also inhibit certain enzymes. These factors are well described in cartilage in general, but specifically shark cartilage.

An intriguing trial in Mexico involving six patients piqued my interest. Then I was part of a 20-week Cuban trial. Shark cartilage was administered rectally to these patients. We reported a few responses on *60 Minutes* with Dr. Lane. This was enough to pique the interest of certain people in this country, which led to a U.S. clinical trial here. The OAM, newly created, originally recommended that I proceed on to test this in this country using advanced cancer patients, shark cartilage and lifestyle changes.

It took us a fair amount of time to get approval from the FDA. In the meantime we were given permission by the Senate to accrue patients. Off protocol, we looked at about 125, 150 patients. We submitted the protocol in May 1993 and finally got approval in February of 1994. That's a pretty quick turnaround.

The study design was very simple. The patients had to be incurable – that is, all had metastatic disease. They had to have progressive disease – that is, more tumor growth in spite of various treatments. They had to have a life expectancy of at least 12 to 16 weeks. If they were less than that we could not treat them. They had to have prior treatment with chemotherapy, radiation therapy, surgery. These were all prerequisites for getting into the trial. Each one of

them had to have some measurable disease, whether it was a lump, a bump, or some reliable tumor marker. There aren't too many reliable tumor markers. They had to have something measurable that we could follow. They all had to be, on the Karnofsky index, able to take care of themselves, walk around, and do things like that.

Those who were not eligible for the study included patients with radiation therapy for primary brain cancer, or radiation treatment within the past 45 days. If they came to us at day 30 after the radiation treatment stopped, we could not use them. They had to be after that, because radiation therapy effects continue on after the radiation is turned off. If they had chemotherapy within the last three to six weeks, they were excluded. If they were using shark cartilage with other treatments, they were excluded. If a woman was pregnant or lactating, she was excluded.

This is an important issue of our study. We looked at the quality of life, which is now one of the major considerations by the FDA of most new treatments. What does the treatment do to the quality of life? We looked at several things. Physical symptoms. Do these symptoms get worse, better, or is there no change at all on the cartilage? Lifestyle changes. Was their performance changed, their general well-being? All these qualities of life were answered by the patient. The doctor, the nurse, had nothing to do with answering any of these questions. The patient every week, every other week, when they saw us, wrote down what happened to them as per their perception of these qualities of life. That's more important than a doctor saying I think you're improved, or not.

We put them on the Ten Point Plan, a lifestyle program we developed in 1981. In our first book, called *Cancer Nutrition* – we talked a little bit about it yesterday. This is various qualities of life, like nutritional factors, no smoking, no alcohol, exercise if they're able to, stress modification. We've done that a variety of ways. They were all given 80 to 90 grams of shark

cartilage in divided doses, orally administered. Overall, in the early days, before the protocol, about a third of the people had a response.

What does response mean? It means that something shrank for a short period of time. Some mass shrank at least half of what it was for at least four to six weeks. It's important to know what the definitions are of all these things. Quality of life was improved in over half of the people. If they had bone metastases, the bone pain subsided in a short period of time. Apparently we did see some antitumor effects, obviously some antiinflammatory effects, and minimal enhancement of the immune system based on some of the parameters we tested for.

We have accrued about 30 patients on protocol. We're seeing overall about a 15% response rate, which means that 85% of the people did not respond. The people who did respond, the 15% responders, had at least a shrinkage of the tumor by about half for at least four to six weeks. That's the definition of response. 15% of the time people modifying their lifestyle together with orally administered shark cartilage had a response.

The criticism I have of this study, my own study, is could the lifestyle changes alone be operational here? As we saw yesterday when I spoke about breast cancer, whether you take chemotherapy or hormonal therapy, the results are about the same. The overall life span in those patient groups are about the same, since 1930. But if those women changed their lifestyle, they actually lived longer. It's critical to change lifestyle. Backing up to this study with the shark cartilage and lifestyle changes, what is operational? Is it shark cartilage? Is it lifestyle? Is it a combination? As a scientist, I have to say that it's the combined effect, because I can't pick out one or the other. But we do know that lifestyle changes have a dramatic effect on the reduction of tumors per se.

Several issues came up yesterday. Some people are still here and still in a quandary. I'm going to talk about that now. If there are any questions, you can address them. We talked yesterday about whether certain vitamins and minerals should be used during chemotherapy, radiation therapy. Most doctors – Dr. Weil, Dr. Larry Norton, and many of the leading doctors around the country – say don't use vitamins and minerals during radiation and chemotherapy.

There are over 200 references that show that they should be used, in the medical peer-reviewed literature from the 70's, 80's and 90's. There's not one published peer-reviewed article, not one published abstract, that shows vitamins and minerals interfere with chemotherapy or radiation therapy. When you have a belief system, you go to a church and synagogue. When you're talking about science, you look at the scientific data. That was one issue.

Another issue was about soy and its relationship to breast cancer patients. Soy products, and soy, in fact, have estrogen-like compounds in them. That's what exerts a positive effect on a post-menopausal woman, decreasing post-menopausal symptoms. Soy, with its positive estrogen-like effects, may be harmful to a breast cancer patient. We're not talking about prevention now. We were talking about cancer treatment yesterday. The question arises always, should a breast cancer patient take soy products?

There are no data at all to address what I'm going to tell you, although there is a protocol, a study being looked at now. There are no data to say what I'm going to say. Right now I would err on the side of being conservative, rather than err on the other side. Anyone who has breast cancer should avoid soy products until we know that soy products are not harmful to the patient. Any other questions? Any questions at all?

Participant: (Did not use microphone.)

Dr. Simone: Yes. Dennis Miller borrowed my protocol, and that was the extent of what he did with the protocol. He just borrowed it. I never saw any of the patients, never saw any of the data. I don't even know if the data, if the study was done to what we had written with the FDA. They published the abstract in ASCO showing that they were all negative patients. I really can't comment on any of the details of it. I was never part of it, even though they "used" our protocol.

Participant: (Did not use microphone.)

Dr. Simone: There are a number of studies now to suggest in animals that leukemias might respond equally favorably with cartilage preparations. That's in animal studies, not human. Dr. Lane?

Dr. Lane: Yes, I wanted to comment. For those of you who would like to be brought up to date, there are two, I should say three FDA trials going on right now on stage IV patients, phase II trials. Two of them are going on in northern New Jersey, one on brain, and one on breast. In the breast study, the first four patients have reached 20 weeks. Of those patients, two have not responded, one has shown complete stability, and one has shown – she had major mets in her lungs. They have all disappeared. She had a major tumor on the neck that has been reduced by 30%. It is now 28 weeks. I'll be getting the 28-week figures when I get back from that trip.

You also ought to know that in Chicago, Northwestern University is going to be running a brain study. That study is starting immediately. If anybody is interested in getting into it, the protocol calls for patients who have failed at least two therapies. They have to be off all therapy for three weeks. Then they have to use this as the only therapy.

The difference between my protocols and the one that Chuck Simone has talked about is that in these therapies the shark cartilage is used as the only therapy. There are no vitamins, antibiotics. There's no restriction on diet at all. In fact, in the Cuban trial and in the Mexican trial which were referred to, there were no restrictions on diet. All of them had pretty poor diets.

Participant: I had two questions. First, you mentioned the patients that were pre-FDA approval of the trial. Were they treated exactly the same as patients that were officially on the trial?

Dr. Simone: I treated them as if they were on protocol. However, I could not actually control for their behavior outside our office. I wanted them to have no chemotherapy, no hormonal therapy, no other adjunctive alternative medicines. But I couldn't control that. I didn't know what was exactly happening. I don't know what happened to them. That's why there was a pre-protocol approved study and a post.

Participant: So you can't actually tell if there were other treatments? You weren't able to find out from them?

Dr. Simone: I asked, but it wasn't reliable information, I thought at the time.

Participant: Also, for patients who have responded in your estimation, can you comment on the types of tumors that responded and if there's any trend in what kind of tumors are responsive?

Dr. Simone: The several responses that we did see were in primary brain, breast, prostate – no head and neck, no lung. Those were the major ones that we saw responses in.

Participant: Dr. Simone, as a gastroenterologist who does pharmaceutical research, I'm curious why you didn't use rectal administration. There are a lot of pitfalls when you give things orally. You have to go through the GI tract. I've done a lot of research on things like 5ASA and we know that there's tremendous absorption in the sigmoid colon. I'm just wondering if the Cubans did it, why didn't you?

Dr. Simone: We were part of the Cuban study. To make sure that they got the treatment when we were gone. We weren't there every day. We administered it rectally. Patients have a great aversion to rectal administration of anything. How many here want to give themselves an enema three times a day? All your patients do? Well, most patients have an aversion to dealing with the rectal area of their body. They found it much easier to take orally. Oral administration of molecules – you can absorb 50,000 dalton molecules in the GI tract very easily. I don't think the absorption of the activity was an issue when it was given orally.

Participant: (Did not use microphone. Question was about vitamins and minerals with chemotherapy and radiation.)

Dr. Simone: 200 references show that there's no interference, and actual enhancement, and decrease of side effects. That was a point I made yesterday that I wanted to bring back again for anyone who was here from yesterday's talk.

Participant. You said no enhancement?

Dr. Simone: There is enhancement of the modalities of chemotherapy and radiation therapy with nutrients on board.

Participant: Do you know of any data on combined use of bovine and shark cartilage?

Dr. Simone: I do not know any data combining bovine and shark cartilage together.

Participant: (Did not use microphone.)

Dr. Simone: Were there any patients in my study with colon cancer? There were. They did not have a response.

Dr. Kronenberg: Our next presenter will be Dr. Zhuang from China. He received his initial training from the China Pharmaceutical University and then his PhD from Gifu University

in Japan, where he also conducted research for quite a while on mushrooms, seaweeds, etc. He very recently moved to New Jersey where he is a chief researcher at the New Jersey Bio Research Institute. His particular interest has been carbohydrate chemistry, particularly utilization of polysaccharides. Dr. Zhuang will do his presentation. English will be a problem in answering your questions. He asks that if you have questions, please write them on a card. Include your name and address, and if you have an e-mail address in particular. He could then get back to you and respond specifically by that mode of communication. Dr. Zhuang.

Dr. Zhuang: Good morning. It is my great honor to be here and have the opportunity to talk about the medicinal mushrooms, especially Maitake D-fraction. I studied at China Pharmaceutical University, and Gifu University in Japan. My specialty is polysaccharides obtained from various mushrooms and seaweeds. Today I'd like to share with you some information on the biological activities of mushrooms. I came to this country just a few months ago, and this is my first attempt to make a presentation in English. You may have a tough time understanding my English, but please bear with me.

*(Here follows a full version of Dr. Zhuang's paper, with additional information presented in person inserted where appropriate.)*

There is an old Chinese and Japanese proverb which states that, "Medicine and food have a common origin." Mushrooms are examples of foods which health-minded people enjoy. Mushrooms are a significant source of physiologically active compounds that have been studied for the development of some natural medicines.

Mushrooms have also been used as both food and medicine since very early times. However, the efficacy of these medicinal mushrooms was not clearly established by modern science until about two decades ago. In the 1970's, Japanese researchers isolated naturally-occurring polysaccharides from certain mushroom species that were free of the serious side effects associated with conventional cancer chemotherapy (anti-carcinostatics). Their antitumor effects were largely attributed to immunological enhancement. Three anti-carcinostatic biological response modifiers (BMR) were developed from these mushrooms and approved by the FDA in Japan for cancer treatment.

In 1977 a Japanese chemical company developed the first polysaccharide anticancer drug called Krestin or PSK for oral administration. It is based on beta glucan and a protein compound obtained from Kawaratake (*Coriolus versicolor*). PSK must be the best selling anticancer drug in the world. Shiitake (*Lentinus edodes*) is the most popular mushroom in Japan. In 1985 a Japanese food company succeeded in extracting the beta glucan and obtained approval from the Japanese FDA for use as an anticancer drug. The drug is called Lentinan, which is good for gastric cancer by injection. Another Japanese company developed the third polysaccharide-based anticancer drug approved by Japan FDA, Shizophyllan, from the Suehirotake mushroom (*Schizophyllum commune*). This is a pure beta glucan and is used for cervical cancer by injection.

These have been sold predominantly in Europe and Japan. However, Japanese scientists identified another mushroom known as Maitake which is even more potent than any of the other mushrooms previously studied. This legendary giant mushroom has been studied for its anticancer, antidiabetic, antihypertensive and antihyperlipemic effects since the mid-1980's. Its

anti-HIV activity *in vitro* was demonstrated in tests conducted by the Japan Institute of Health and the U.S. National Cancer Institute in early 1992.

Among various extracts obtained from the Maitake mushroom, a specific extracted fraction named Maitake D-fraction is the active constituent. This extract contains beta-1, 3-glucans and beta-1, 6-glucans protein-bound polysaccharide. It has demonstrated remarkable antitumor activity by activating the immune system through oral administration. Additionally, animal studies have shown that the dried crude powder appears to exert antihypertensive, antidiabetic and antihyperlipemic effects.

1. Inhibiting Tumor Growth. The effects of Maitake D-fraction on immune-competent cell activation was investigated. Two groups of mice were given either 0.5mg/kg of D-fraction by i.p. (intraperitoneal) administration or 1.0 mg/kg D-fraction by oral administration for 10 days. Natural killer cells (NK), interleukin-1 (IL-1), cytotoxic T cells (Tc) and superoxide anion (SOA) were measured before D-fraction administration. NK cells and Tc were increased 1.5-2.2 times compared to baseline by Maitake D-fraction. Also, it was observed that the production of IL-1, which activated T-cells, and SOA, which damages tumor cells, were significantly enhanced by D-fraction. Also, in mice injected with D-fraction for 10 days after implantation of Sarcoma 180, the tumor inhibition rate was 80.2%. From these results, it is evident that inhibition of tumor growth was due to the cellular immune system activated by D-fraction.

In these tests, mice were injected with D-fraction from Maitake, Lentinan from shiitake, and PSK from Kawaratake for 10 days after implantation of Sarcoma 180. The tumor inhibition rate of Maitake D-fraction was 86.6%. Lentinan showed weaker inhibition effect. PSK had no

effect, because PSK is designed for oral administration. As you see, the size of the tumor was much bigger in the control group. We cannot see tumor in the D-fraction group any more.

This is an example of a clinical case using Maitake D-fraction on a patient with brain tumor. He had received chemotherapy in four cycles, but he could not accept it because of serious side effects. He received no treatment for four months before starting Maitake treatment. After four months of taking Maitake D-fraction, this cancer focus completely disappeared.

2. Inhibition of Cancer Metastasis. Preventing the metastasis of cancer from one area of the body to another is an important concern in cancer treatment. A test was conducted in the following manner: MM-146 liver carcinoma was injected into the left rear footpad of mice, and the footpad was cut off after 48 hours. The mice were divided into three groups and fed A) a normal feed; B) a feed consisting of 20% Maitake powder; C) a normal feed with 1mg/kg/day Maitake D-fraction (i.p.) for 10 days. All three groups were bred for 30 days. The result showed that metastasis to the liver was prevented in 91.3% of the animals by the administration of D-fraction and in 81.3% of the animals by the oral administration of Maitake powder.

3. Prevention of Carcinogenesis. This study investigated whether Maitake D-fraction can prevent experimentally induced carcinogenesis in normal cells. N-nitrosodi-n-butylamine, a potent carcinogen, was added to the animal feed in a dose of 1 mg/day, 3 times at 7-day intervals. Group A was fed with normal food; group B was fed with a feed containing 20% Maitake powder; and group C was orally administered 1 mg/kg/day Maitake D-fraction for 30 days. After 60 days, the occurrence rate of liver cancer was 9.7% in the D-fraction group, 22.2% in the Maitake powder group, and 100% in the control group. These results suggest that D-

fraction may be helpful in reducing cancer risk from exposure to some of the chemical carcinogens in our environment.

4. Synergistic Effect with Chemotherapy. Unlike many conventional anti-carcinostatics, Maitake D-fraction does not kill cancer cells directly. It activates immune-competent cells and lets them fight against cancer cells. Mitomycin (MMC) is probably one of the most popular chemotherapeutics used to treat various forms of cancer in Japan and America. In this test, one group received D-fraction, another MMC and a third group both Maitake D-fraction and MMC (cutting each dose by half). All were injected into tumor bearing mice. After 30 days, D-fraction alone inhibited tumor growth by 80% compared to 40% inhibition by MMC. When MMC and D-fraction were given together, tumor inhibition was further enhanced by almost 98%. These results seem to indicate a synergistic effect between MMC and Maitake D-fraction in killing tumor cells. A possible explanation may be while MMC attacks tumor cells, the immune system is activated by Maitake D-fraction.

This is the summary of the results of a non-control study using Maitake D-fraction against 165 cancer patients. The criteria to judge the effectiveness are established as one of the following: A, if the size of tumor in CT or MRI screen reduced or stayed unchanged. B, if the value of tumor marker decreased. C, if T, N or M factors reduced or remained unchanged. D, if the remaining life expectancy indicated by the doctor was prolonged by more than four times. As you see, these results suggest breast, lung and liver cancers were clearly improved by maitake D-fraction alone or both chemotherapeutics and maitake D-fraction.

5. Anti-HIV. Both Japan National Institute of Health and U.S. National Cancer Institute demonstrated that Maitake D-fraction was able to prevent HIV-infected T-helper lymphocytes from being destroyed by as much as 97% *in vitro*. This is important because measuring the T-helper cell count is one way to trace the progression of HIV to full blown AIDS. It has been estimated that approximately 40% of the patients with advanced AIDS will develop Kaposi's sarcoma (KS). An effective treatment has yet to be found. Recently Dr. David Hughes in San Bernardino, CA, has reported success in treating KS with two-thirds Maitake D-fraction liquid extract plus one-third DMSO (dimethylsulfoxide) applied directly to lesions not more than four times daily.

6. Antihypertension. A group of spontaneously hypertensive rats (SHR) were bred on feed containing 20% crude Maitake powder (whole ground mushroom). In contrast to the control group (in which the blood pressures increased with age), the Maitake group experienced a significant reduction in blood pressure. When the Maitake group was returned to its normal feed without Maitake, blood pressure increased. However, reduction in blood pressure occurred again when the animals were put back on the feed containing Maitake. These results suggest that Maitake mushroom powder appears to have a blood pressure lowering effect.

7. Anti-diabetes. In this study, a group of female KK-A<sup>y</sup> mice (spontaneously diabetic mice) were fed a diet containing 20% crude Maitake powder for an eight-week period. Levels of blood glucose, blood serum insulin and blood serum triglycerides in the Maitake group all remained significantly lower than those in the control group (those not consuming Maitake).

The same result was shown in a cross-over experiment. These results suggest that Maitake mushroom powder appears to have a glucose lowering effect.

8. Antihyperlipemia. One group of five-week-old rats were fed hypercholesterolemic diets and another group was fed the same diet plus 5% crude Maitake powder to examine the effect of Maitake powder on lipid metabolism. In the Maitake group, total cholesterol in plasma lipids was reduced by 24.7%, total cholesterol in liver lipids was reduced by 7.0%, and body weight was reduced by 16.5%. These results suggest that crude Maitake powder may be useful for lowering cholesterol levels and body weight.

9. Conclusion. Since the cultivation method of a Maitake mushroom was established in the mid 1980's, this mushroom has gained much popularity among the Japanese people. Its medicinal value has been elucidated by many researchers in the last decade. Maitake D-fraction demonstrated remarkable antitumor and immune enhancing effects when administered orally, unlike many other mushroom extracts that must be injected to exert these effects.

Human clinical trials, animal studies, and case reports have demonstrated that Maitake D-fraction appears to be remarkably effective against cancer of the breast, lung, liver, prostate and brain. Also, both animal studies and clinical cases demonstrate the synergistic effect with chemotherapy while improving serious side effects from chemotherapy. Hopefully, more attention will be paid to natural nontoxic therapies as a first line, rather than the last line of defense against cancer. Many natural therapies, including D-fraction, appear to have a significant impact upon cancer without harming the immune system or normal cells.

Though the data is preliminary, the results of animal and limited clinical studies on Maitake D-fraction suggest a powerful healing and preventive potential for cancers. In February of this year a New Jersey company obtained its IND from the FDA to conduct the phase II trials study on the effect of Maitake D-fraction on advanced breast and prostate cancer patients. This is a giant step for proof of nutraceuticals from the Orient to the American public, including medical professionals.

Dr. Kronenberg: Thank you. Now we'll have some comments from Dr. Preuss, who is a professor of medicine at Georgetown and president-elect of the American College of Nutrition. His particular interests are in the cardiovascular system and hypertension and nutrition. He'll make some comments on the various presentations. Then we can open the floor up again for further questions from the audience. There are index cards available so you can hand in your questions to Dr. Zhuang. Thank you.

Dr. Preuss: When put in this position, I tried to figure out what I was going to say. As I was listening to some of the presenters, I noticed some in the audience were very sharp and were asking the questions that I was asking in my own mind. I will attempt to be brief.

I enjoyed the last talk on the Maitake mushroom primarily because Maitake mushroom has a number of effects, not only on the cancer cells but on type 2 diabetics and on hypertensives. When I looked through the literature doing my own work on hypertension, I was intrigued to find out there were connections, although weak, between people who develop hypertension or people who had diabetes and glucose intolerance, and cancer formation. One of my first thoughts was that somehow this is very effective because it works through that system.

If you do have insulin resistance, and in some forms of hypertension the insulin levels rise – they are primary growth factors; insulin-like growth factors also rise – this could be a pathogenic mechanism.

The question I would have asked Dr. Zhuang (I don't know whether he could answer it or not), is when they take whole Maitake and fractionate it into the D-fraction, does this still possess those properties on these other characteristics? I know they do have separate fractions that have effects on diabetes and hypertension. We are studying them in the lab. We're beginning to see those effects. But I would like to know, as you fraction along, the decisions, the other fractions, what effects do they have compared to these effects? I'd be very interested in that.

I was also interested that in each of these talks we were describing different mechanisms to attack the tumors. In this particular one it appeared to be perhaps an immunologic response going on. In a previous talk, someone talked about how wonderful DNA is and how well DNA can change and try to survive. These little cancer cells seem to be better than our normal cells. They're all the time trying to find a new way to survive and bypass it.

As an amateur, it seems to me that in cancer chemotherapy we're going to have to put a number of approaches together. We're going to have to attack it. Perhaps we'll attack it at an angiogenic level. Perhaps we'll attack it with a virus. Perhaps we'll attack it with Maitake. We'll have to put them all together, because these cells have ways to keep escaping. It looks like we have to work on this.

Immunology enhancement was an interesting concept. In the studies with mitomycin, there seemed to be an additive effect. They didn't see a synergistic effect, but an additive effect. Perhaps that's saying the same thing that I'm coming across with – you have to have the basic

effects of the Mitomycin and then an immunologic stimulus and attack it. All of those things come into play.

I very much enjoyed Dr. Simone's presentation. It was clear, and he told it like it was. As I was listening to him, and the previous speaker, the first thing that came to my mind was the original talk someone had made about mental abilities and lifestyle. I was thinking, is it the shark cartilage, or the lifestyle changes, or both? He answered that. He came through.

I had the same question with the virus. It was very clear-cut. It's an exciting field. Another way to try to attack the tumors. Prevent the blood from going there. Prevent their nourishment, their oxygenation. This may have an effect. A month or two ago other angiostatic mechanisms were coming out. They're looking at other agents that work on them, trying to find the best one. When the press was really hyping it, the investigators said, to their credit, "Yes, it works on mice." He was very clear-cut. That's not to discourage us, but we have to keep everything in perspective.

Dr. Simone, someone brought this up previously, too. We take the worst patients and try the therapy on them. I always tell medical students that if somebody's got a scar, I can't do anything about it. One of the precepts of being a physician is you do no harm. You have to weigh everything, the risks and benefits. You try it out in the worst scenarios, where perhaps other therapies have been tried. Nothing works. These individuals have nothing to lose. You'd feel very badly if you took people early in a disease – not only cancer, but anything – and started to treat them with something, and found a toxic effect. We are a little hesitant to do that. We have to look at risks and benefits. We have to decide. Unfortunately, this is the way it comes out. We handicap ourselves. Then again, if in these very severe patients we find any ray, then

we start going down the scale. We work on people at earlier stages, to convince ourselves about the ultimate toxicity there.

I was very interested in the effects of the viruses. What ran through my mind was, how do you choose a virus? They chose to do no harm, to pick something that wasn't harmful to the individual. If I were starting a project like this, I would have been a little frightened. They picked patients who are immunocompromised. I'd say maybe a virus appears to be nonpathogenic, but what is it doing in a cancer patient or hepatitis? We have the evidence that it seems to be very safe, so it worked out. If data like this continues, you'd have to look to see whether there were better viruses out there, and which tumors they affect.

This is always a problem. I mentioned yesterday that I've been the chairman of the risk/benefit committee at Georgetown for ten years. I've looked at every human cancer protocol coming across the desk. I always laugh with them because they talk about other forms of research. Everybody gets a little haughty about his area of research. I'll say, "Yes, you're going to give the patient x and y, and if that doesn't work you're going to take y away and give z." Even though I'm a little cynical about it, I realize it's necessary. It's very difficult, with the number of tumors out there, to try to pick that magic bullet. If we look at standard medicine, for every tumor there seems to be a different procedure to attack it. There's not going to be one overall therapy. Each tumor is going to have to be individualized, and it's going to take a number of different ways to attack it.

I was interested in the fact that the viruses work on hepatitis as well as on tumors. That came across to my mind. Why does that work that way? Perhaps it was touched upon. We talked about the theory of apoptosis, programmed cell death, where there is a program in that cell that causes it to die. When a cell is injured, something may take over and tell it to eventually

die. Can we control this mechanism? Can we somehow tell cancer cells to die? There have been various theories about why some complexes work on the basis that they stimulate apoptosis through very fine mechanisms of affecting this particular protein or that protein. Perhaps the viruses are working in that sense. That would be exciting. We're going to be looking at this in the future. Having repeated what the panel already said, let me end. We'll open up for questions.

Dr. Kronenberg: Are there any additional questions to the panelists? Please address the floor from the microphone.

Participant: Dr. Preuss, it occurred to me, it's been over and over again at all the presentations, why do these people have to be three-quarters dead before any of these alternative remedies can be tried? I understand exactly where you're coming from. But there's also a great call for empowerment of the cancer patients themselves. Do you think the medical community will ever have the courage to let the patient decide to get into something like this a little earlier, so that they can have that control over their life?

Dr. Preuss: Oh, yes. No doubt about it. But don't blame the medical community...

Participant: Maybe a less leading question is, what would it take to get the medical community to be more responsive, to move in that direction a little quicker?

Dr. Preuss: The point I was trying to make is don't just blame the medical community. As a young intern and a resident we were often faced with the question of when do you let the patient go? It's a very difficult decision. It depends on your ethics, your background. It's not easy. Doctors were always criticized for this. I was asked by patients' families to let them go, even sometimes when I thought I could save them. Let them go. I never really handled that problem.

I did take some solace that when these cases would go before judges, I'd find that they were having the same problems we were. Put yourself in that position and think about it. It is difficult, if you have a new form of therapy and there is any potential for some hazard, to put it onto somebody who has the chance, if they go some other way, to bypass this. Yes, if the study is designed differently, we'll change. If a patient were to come up to me and say, "Go ahead with it," yes.

On many a Friday night late in my office I got a call for a compassionate use of a drug. Most of the time it turns out to be for some child. I'm stuck there with that decision. I've looked at the records, and everything has been done that possibly could be done. You're right. As soon as they test at different levels, they will come up. But think of doctors as being like everybody else. I'm sure if you were put in that position – it's easy to look there and say, "That's what I'd do." When you're the final judge, yes or no, then you think, "Oh my gosh!"

Dr. Simone: It's not only the doctors. It's the legal community and also the FDA. The FDA says for a new substance to be used, you have to do it on this type of patient. The exclusions are people with renal cancer and melanoma. You can treat them with new investigational agents because we have no effective treatment at all. That's why the FDA

approves it. Those are the major exclusions. You can use any new agent on those patients without prior treatment.

Participant: I'm curious for the virus treatment if it would be possible to use it as adjuvant therapy after all of the primary tumor has been removed, especially in cases where there is no known effective adjuvant therapy, for example, renal cancer, which I happen to have.

Dr. Bakács: Yes. All of the patients whom we treated were on conventional therapy. There was no problem that the patient received the conventional therapy, and when conventional therapy failed, started the virus treatment. But if the patient for any reason went back to conventional therapy or was on conventional therapy still, the virus treatment could be started. There was no reason not to start except that the legal rules are strict in these cases.

Participant: In this country, with renal cell cancer and melanoma you can use any treatment you want, provided the FDA has an IND for it. If this program was in this country you could start that from the get-go. Would that be true as adjuvant therapy for renal carcinoma?

Dr. Simone: I think you need measurable disease in all these.

Participant: You're talking then about advanced disease, but I'm thinking something as nontoxic as these viruses apparently are could be used for prevention of recurrence in patients who don't have advanced disease and might have an excellent chance of benefiting. A trial of that sort could be designed.

Dr. Simone: In that situation there's no way you could measure the effect. Is it going to work or not? Can you drink water and get the same effect? You need measurable disease to find out if a treatment is exerting an effect.

Participant: Normally it would be a randomized trial and you'd have to look at the . . .

Dr. Simone: You don't need a randomized trial.

Participant: The Southwest Oncology Group Cooperative Clinical Trials Group is just beginning a series of protocols in which they try various treatments during the time between the biopsy and diagnosis of prostate cancer and the surgery, any prostatectomies. They're trying to see if they can see an effect during that period of time before the surgery. This is a new path that they're trying in research design. I'm not with Southwest Oncology Group, but I have heard a lecture about that. Specifically they're trying out lycopene, which is a substance in tomatoes and red grapefruit and various other things.

Dr. Simone: What's the end point?

Participant: The end point is to see if the resection tissue sample shows the effects of this change in diet. They have a number of things the pathologist looks at.

Dr. Simone: My e-mail address is [drsimone@erols.com](mailto:drsimone@erols.com).

Dr. Kronenberg: I'll give you Dr. Zhuang's e-mail address in a moment.

Dr. Preuss: While they're doing that, there was a question that came from the audience. It kind of hit me when Dr. Simone said it. They were asking whether all the speakers agree that there has been no outcome progress in cancer therapy since the 1930's.

Dr. Simone: It's not a question of agreement. It's what the data show. The NCI puts out data every year from the SEER Information Group, and that gets published by the American Cancer Society once a year, in the January/February edition of their journal, called *CA: A Journal for Clinicians*. It's not open for interpretation. That's what it is.

Participant: I understand what you're saying, in view of the overall statistics. But if you take specific patients with breast cancer and colon cancer – we have done randomized studies with chemotherapy and alternative regimens. When you look five years or ten years down, survival among even those randomized studies have proven successful. I agree with you that when you look at the overall picture we haven't made a dent in cancer mortality. But in specific instances, it's a gross overstatement to say we've made no progress.

Dr. Simone: I didn't say we made no progress. We made no progress in the survivorship of adult cancers. Children's tumors are very different.

Participant: With lung, breast and colon, if you define specific subsets of patients in randomized studies, we're seeing survival benefit. We're seeing quality of life benefit.

Dr. Simone: Wait, wait, wait. Quality of life is a different issue. Does the patient live longer?

Participant: Even in survival we see a definite benefit, even though it's very modest. I don't think anybody would argue that there's benefit, in those defined subsets of patients.

Dr. Simone: I think a lot of people would argue it. It's written all over the *New England Journal of Medicine* all the time. Cancer remains undefeated. It goes on and on.

Participant: Even in that there were pros and cons in the *New England Journal*. People took different sides. It's certainly debatable. I still get back to the point about defined populations. I don't think it's any longer debatable that there are survival benefits within defined populations with intervention with standard chemotherapy.

Dr. Simone: Then what you need to do for this audience is define your definition of cure. If a patient lives five years and a day, the patient is cured in the textbook, but the patient is dead.

Participant: I'm not talking about cure. I'm just talking about simple survival curve.

Dr. Simone: That's what cure is, right, survivorship, length of life? How long does a patient live?

Participant: Right. There is survival benefit. I'm not talking about cure. I'm looking at survival curves. I'm seeing there's a difference in survival curves between treated and untreated patients.

Dr. Simone: I'm just going on what the data show.

Participant: So am I.

Dr. Kronenberg: Obviously these discussions can keep going. I have one other question for Dr. Simone from the floor. Has the shark cartilage product used in the studies been standardized? How was the 70 mg dose chosen? Or is it grams?

Dr. Simone: First, when you apply to the FDA for an IND, you have to demonstrate a standard product each and every time. The FDA in this instance would go on surprise visits and check the quality of the particular product used. The product used in a certain protocol must always be standardized. That doesn't mean that you can go over the counter and buy a similar product. There are about 60 different products over the counter.

The dose choice is simply based empirically. We looked at studies. When I looked at the six patients in Mexico, 40 mg didn't do anything. When we started studying Cuba, we looked around 60-70 grams per day. Then we escalated up to 80. It was terribly empirical.

Dr. Kronenberg: I want to comment on the issue of standardization. In a lot of these studies, be it shark cartilage, any botanical product, etc., particularly if they are studies that are initiated and funded by the NIH, they are usually using a standardized product that a particular company or group has made. Let's take St. John's wort for depression. NIH has just funded a three million dollar study to look at St. John's wort, a particular formulation by a particular company. Let's say that the results of this study, x years from now, prove that this is beneficial for depression. Does that mean you can go to a health food store and pick up any package of St. John's wort and it will have a similar effect? The answer is probably not. Right now the quality control in this country is not terrific for any kind of dietary supplement, botanical products. If you had pure St. John's wort, would it work? The answer is probably yes. But right now the regulatory process is such that some of the companies make terrifically good products and some of them don't.

There's a study being done right now by the American Botanical Council. They went around the country into 400 stores and picked up 400 different permutations of ginseng products. They sent them to independent laboratories in the United States and Canada to see how much ginseng is really in each product. The results are shortly to be published. First they sent the results back to the company so the company could respond and say why their ginseng product didn't have any ginseng in it.

Of course, the company says, "We don't make that product any more. We now have another product." The bottom line is that doing things like this will make companies become more responsible. A lot of the industry who is responsible would like to see others toe the line. It's difficult for consumers to go out and purchase products based on the result of a study which

is using a different product. Some of these things will be available on the market. For others it will be difficult until quality control becomes a little better in the United States. This will happen over time. Right now it's really difficult.

Participant: (Did not use microphone.)

Dr. Kronenberg: The issue that also comes up with respect to standardization is what does that mean? For example, St. John's wort is standardized to .3% hypericin. However, the thought is that hypericin is not what is responsible for the effect. Right now standardization is just taking a marker that you have that product. It's really St. John's wort. We know it's St. John's wort because all St. John's wort has this peak. But you don't know that that's the active ingredient.

A lot of people working in the area of botanicals are interested in the question of whether the whole is better than the sum of its parts or than any one part. Some people would say you can take a part out, find out which is most active, and give that particular component. Other people are of the opinion that one needs the different synergistic effects. Further, if a particular product has a beneficial effect that you're looking for, but also a negative effect (it makes your blood pressure go up or something), perhaps there are other components in the plant that are controlling that.

People give the example of digitalis, which has a very narrow window of therapeutic efficacy versus detrimental effect. If you eat the leaf, you will get nauseous before you would have a detrimental effect. Then some of these things are very nice to be able to control because they may be more difficult to use. The question of whole versus isolated extracts is up for

investigation. I have heard about studies, for example, looking at allicin from garlic, showing that garlic as a whole has a much more beneficial effect than just taking the allicin. Again, it's effect on what? This whole area is up for discussion. I would love to see research in this area. That brings up the question of what are you standardizing for, and is it meaningful? We don't have all the answers to that, but they are important things to think about.

Dr. Simone: Germany has tried to do that with the Commission E report, but it still has not met the standards we need.

Dr. Kronenberg: Let me give you Dr. Zhuang's e-mail address. It is [maitake@intact.com](mailto:maitake@intact.com). You can e-mail him any questions that you have, or bring your questions up, and he will respond to you. Are there any additional questions?

Participant: There's the same question with generic drugs. The problem with standardization is the same problem with getting FDA approval, or the same problem in getting an IND. These things are not done by government to prevent you from getting treatment. It's to protect you from getting bad treatments. We all as a group when we hear about alternative therapies need to understand that some of these things are there for a reason.

Dr. Simone: Yes. When possible it should always be held to the same scientific rigor. Now some of these things can't – massage therapy, things like that. But if it's a drug-related compound, or something like a drug, it should be held to the same standards.

Dr. Kronenberg: Not only do you not know whether there's really ginseng in the box, but sometimes there are contaminations, both intentional and unintentional. Some of the formulas imported from other countries have pharmaceuticals in with the botanicals. Sometimes it's misidentification of plants. In some cases what were reported toxicities of a particular herb were in fact not a toxicity of that herb, but a toxicity of a misidentified herb that had been sold as that herb. All of these issues are of concern. There are responsible people who are interested in dealing with those issues and making products that are of high quality and of known quality.

Participant: (Did not use microphone.)

Dr. Simone: We've improved our cancer therapies in that age group very significantly.

Participant: I realize that, but my question is why? Why is it possible to make those improvements in childhood cancers, whereas it has not been possible with adult cancers?

Dr. Simone: Not all childhood cancers, but the majority of them. We see improvement in the great majority of them mainly because they respond very nicely to the chemotherapies or the radiation therapies in a way that the adult generally does not.

Dr. Kronenberg: I thank all of you and our speakers very much.