

Comprehensive Cancer Care: Integrating Complementary & Alternative Therapies  
Immunotherapies

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Session 105: June 12, 1998

Dr. Dattner: I'm a dermatologist. I've been doing alternative medicine for about 19 or 20 years. Before that I was a research immunologist at the National Cancer Institute. I've done a lot of work with cellular recognition, so I've had a look at both sides of the fence between alternative medicine and conventional advanced immunological research.

Dr. Freeman has to leave early, so we'll take a few questions for him after his talk. We'll take the remaining questions after all presentations are complete. We will have a commentator at the end of the presentations, Dr. White. We're trying to get viewpoints from both sides, although I think you'll notice that some of our alternative presenters have spent a fair amount of time within the conventional realm at research institutes.

Let me talk a little bit about our first speaker, Dr. Arnold Freeman. I can't possibly go through all of his CV. He has quite an extensive background. He has served as chief of the Department of Hematology and Oncology at Children's Mercy Hospital in Kansas City and Professor of Pediatrics at the University of Missouri for 11 years. In the past he has had numerous positions involving pediatrics and research in such places as SUNY-Buffalo, Children's Hospital in Buffalo.

Dr. Freeman serves in numerous professional societies including the American Association for Cancer Research, the American Society for Clinical Oncology, the American Society for Hematology, the New York Academy of Sciences, and more. He's also chairman of a number of protocol committees, including the Cancer and Leukemia Group, three different

ones for brain tumors, non-Hodgkin's lymphoma and acute lymphomas. He's been chairman of numerous other studies and a member of many boards. He has written over 131 papers and numerous book chapters. Without further ado, I'm going to introduce Dr. Arnold Freeman.

Dr. Freeman: Thank you very much for that beautiful introduction. Both my parents are dead. My father would have loved that introduction. My mother would have believed it.

I would like to start with treatment with Newcastle Disease virus in high-grade gliomas. We have four children who I'm going to present. These are patients treated in Israel; this slide shows the background of Hadassah Hospital and the Hebrew University.

The use of viruses to treat cancer is not new. There are reports dating back to 100 years ago when investigators found that patients with cancer who underwent concurrent viral infections had a remission. It was not a common event. It was a rare event, but it occurred. Half a century ago investigators found that if they had a mixed culture, for example, of tumor cells and normal cells, and then they added virus to it, the virus would selectively destroy the tumor cells. Later, in the 60's and 70's there were several studies of viruses in cancer. Those studies are imperfect but nonetheless seem to show that certain viruses were effective in the treatment of cancer. This is bacteria (I believe it's *E. coli*), and it shows you the size of the bacteria. It looks like a monster compared to the virus; viruses are tiny.

This is the virus we're going to focus on. It's a paramyxovirus, which is one of the larger viruses. It's an RNA virus, and it's encapsulated. This is the virus in the flesh. There's the RNA helical base. It's covered by capsids, and then there's a lipoprotein envelope around it. The little projections are probably very important proteins that allow the virus to attach to different cells. The Newcastle Disease virus is this virus. The Newcastle Disease virus is a

chicken virus that produces respiratory and CNS symptoms in chickens. It probably does not replicate in man, which is a very important feature. If it replicates, it may be only one or two passages. In normal hosts, viruses are obligate parasites that replicate only in the host cell. If the host is not the type they're used to, as with a chicken virus in humans, they generally do not replicate.

These are two background experiments that are very important. They're by Lorence from Chicago, who injected nude mice – mice without any immune system. After there was tumor on the surface, he treated these mice with direct injections of the Newcastle Disease virus. The results here are extremely dramatic. Seventeen out of 18 tumors in mice regressed permanently. All 18 mice that were injected with the so-called placebo, or saline, progressed.

The other piece of very important information from this work is that the dose of virus was critical. He injected mice with  $10^7$  viruses. When he used  $10^6$ , only 25% of the mice responded.  $10^7$  viruses is a large dose. We don't inject anywhere near that in a human being. That was in neuroblastoma, a childhood nervous system tumor that occurs in the periphery of the blood. He ran a very similar experiment in fibrosarcomas and found the same phenomenon.

I now work at Hadassah Hospital in Jerusalem. We at Hadassah Hospital became very interested in the Newcastle Disease virus. Dr. Csatory is one of the fathers of the use of this virus. I flew into Budapest to meet with him and I evaluated their data. Subsequently we treated four patients with high-grade gliomas, with brain tumors. High-grade gliomas are a disaster. For example, the most high-grade glioma is a glioblastoma multiforme with almost 100% mortality and a life survival of one year.

This is a youngster who is probably sitting in the audience. He was born in Russia. He was presented with difficulty in his vision. He was evaluated in Russia and found to have a

brain tumor. This was a glioblastoma multiforme. He was operated, and then he was irradiated. He presented initially in September 1994, and we see the tumor diagnosed. He emigrated to Israel subsequently. In November 1995, a little over a year, there was recurrence of the tumor, which is par for the course in this cancer. By March 1996, four or five months later, he was in terrible condition. He had been treated with chemotherapy in this interval without response. He had a very low functional status as evidenced by the Karnofsky. He was in a wheelchair. He was convulsing. He was on Dilantin. He was sick enough that we asked his father to come in from Russia to visit him. I thought his life expectancy was days or weeks at the very most.

The picture you saw of him is as he is now. In May 1996 he started Newcastle Disease virus. He started it with a vial a day. The dose was boosted to four vials a day, with symptomatic improvement noted very quickly. Those of us who are trained in classical oncology want to see objective evidence. We want to see the tumor shrink. Objective evidence such as tumor shrinkage on the MRI took over half the year. In fact when we saw the first MRI that we did after diagnosis, after progression, we were concerned the tumor was slightly increased in size.

Nonetheless we persisted with the Newcastle Disease virus, and the tumor started to shrink. By September of 1997, the tumor had shrunk probably by about 70%. He remains on the virus. I will show you the pictures subsequently. He is off all anticonvulsants. He attends school. He's a very good student. He's off dexamethasone. The only medication he receives now is this viral vaccine which he receives every day.

This is our second patient. This little girl is 15 years old. She's standing next to her father. She had been on dexamethasone which produced the round face. She's off now. Let's go over her story. She's a 15-year-old girl diagnosed in August 1995 as an anaplastic

astrocytoma. That is not quite a glioblastoma, but it's still a very bad actor. She received chemotherapy, radiation and surgery. By September 1996 there was a recurrence of the tumor. The tumor was again grossly resected. However, within three months the tumor recurred. By April 1997 the tumor looked like a glioblastoma, which has a classical butterfly appearance.

In June 1997 we started the Newcastle Disease virus. One year later, June 1998, she's neurologically improved. She's off all dexamethasone, but her MRI is stable. We have not seen shrinkage of the tumor on the MRI. She's functioning moderately – not as well as the first patient, but she is functioning.

This is the third patient. This is a little boy 3 ½ years of age who was diagnosed in 1995 with glioblastoma of the occipital lobe at 15 months. He was treated with chemotherapy initially, not with radiation. By July 1997 the tumor had recurred. By July 1997 he started the Newcastle Disease virus and the tumor has now been stable for nine months. He is in essence neurologically a normal child. There are no findings on him. The MRI is stable. Again, there is no shrinkage that we could detect. Neither is there growth.

This is the last patient, an 11-year-old female with a somewhat different diagnosis, gliomatosis cerebri. This is also a type of aggressive glioma, a very rare tumor. She was treated initially with chemotherapy and radiation and had a very short-lived remission. By March 1997 we started her on Newcastle disease virus. However, by August she started to deteriorate, and the Newcastle Disease virus was stopped in December 1997. She was dead two weeks later. We classified her as a nonresponder.

This is going back to the first patient. You'll see the measurements that were seen on this patient in the maximal tumor. This was measured by a neuroradiologist. He told me that generally we do two-dimensional or three-dimensional measurements. It was very difficult in

this case because the tumor looked like the inside of a walnut. I'll show the picture in a moment and you can see why. So he did a single diameter measurement taking the maximal diameter. The tumor was six centimeters, then increased slightly, and now has dropped down to two-and-a-half centimeters.

This is the tumor at presentation. If you follow it along, it slowly gets smaller. There's no question this is now smaller, and smaller, and smaller, until this is the standard MRI that we did perhaps a month ago. The tumor is considerably smaller than it was initially. He functions almost normally, with a slight weakness and limp on his right side. This is the film that we took. It's not 100% fair, this film, because this is a slightly different technique, so please understand that. This was the last film, called an MRA perfusion. It is showing that the tumor is really disappearing. It's quite dramatic.

If we look at these cases (these four children with high-grade gliomas), and we look at their diagnosis, and then we look at the initial response to therapy, we see that in the first case the response to Newcastle was significantly longer than the response to standard treatment. In the second case it is almost the same; it's neck and neck. Please see that the responses with three of the four patients with Newcastle continue. The response with the third patient is again longer. In the fourth patient the response is also very much longer, although we classified her as a nonresponder. She received radiation and chemotherapy and she had a response of two months with standard therapy.

If we look at it in pictorial fashion, the green is a response to Newcastle Disease virus, and the pink is the response to standard therapy. The response is longer, sometimes significantly longer, in the patients treated with Newcastle Disease virus. Because of these findings, we

decided at Hadassah we would like to evaluate this in larger numbers of cases and try to do what we consider a scientific study with this virus.

I don't like the term alternative therapy. I would prefer to call this pre-conventional therapy, just like we have pre-clinical therapy experiments in the laboratory. We want to look at this as we look at drugs and at other biological agents – in a very rigid fashion. We're going to look at patients who have no other alternatives, who are far advanced. We're going to look at the molecular changes and the immunological changes that occur with the Newcastle Disease virus.

As I mentioned at the beginning, we do not know the best way of giving this virus. We don't know the optimal dose. We don't know really what the virus is doing. If we can find this out we can develop a better mousetrap. We're going to try very hard to find this out in this study. As I said, the eligibility is patients who have exhausted conventional therapy.

What have we learned from this study? There are several things. One is that the Newcastle Disease virus appears to be active in high-grade gliomas in humans. Please let me state that there are only four cases. This is not a huge number. For this reason it needs rigid scientific evaluation in a significantly larger number of patients. In addition, we need to evaluate how this agent works. How does it work at a molecular level? What immune mechanisms does it evoke? Thereby we can try to develop a better vaccine. Are there questions please? I'm the one who has to leave early.

The question is why do we have to use this agent in far advanced cases? Why can't we treat patients at the beginning of the illness in such a bad illness as glioblastoma multiforme? That's a good question. We always go with something that's proven. With high-grade glioma sometimes it is possible to purchase a year, sometimes even two years of good quality time with

standard therapy. In my mind, it is justified to first use standard therapy, and when that fails, go to something like this. That's at the beginning. If we're able to confirm that this virus in fact does produce good responses in a significant number of patients, then maybe we can move it right up front. But I don't think we can do that right now.

Can this be used for adults? Yes. In fact, we've treated two adults with this tumor, and we've treated two additional children. All are very recent. We weren't able to report on them because it's too early.

How about use for other cancers? It's being used for a whole spectrum of cancers. It has been used for all the common adult cancers, including gastrointestinal tumors, respiratory tumors, breast tumors, lymphomas. It is being used across the whole spectrum with an objective response. I don't want to quote Dr. Csatory's data, but he has done this. He has published this and he reports approximately a 20% objective response rate. By objective I mean partial response or complete response, patients who feel good, who are stabilized for a period of time. In classical oncological definitions, objective responses generally mean partial or complete responses.

Do patients have to visit you in Israel or can they do this in the States? They can visit me in Israel, but I think it's better at the present time to visit Dr. Csatory in Budapest. His first name is Laszlo. Mrs. Csatory is here and she can speak with anyone who wants to speak to her afterwards.

What's the mechanism? Any thoughts on that? There are lots of thoughts. I suppose when very little is known you can say anything, and very little is known about the mechanism of action. There's some preliminary work that has been done by Dr. Bakacs from Hungary and his crew. It probably induces apoptosis in one cell line, which is the cell line from a

pheochromocytoma. Apoptosis, for those who don't know, means cell suicide, programmed cell death. The cell realizes that its life is over, its function is over, and it dies. This induces apoptosis as the end mechanism, at least in one cell line.

Dr. Dattner: In view of the number of other speakers I have to cut questions short. I want to thank you very much.

Our next presenter is Dr. Josef Beuth, who is the President of the German Society of Oncology, an alternative cancer treatment society. It is actually larger than the conventional treatment society in Germany, thanks to the great interest and to his great work pulling together a variety of organizations. He has an interest in a lot of different areas – in lectins, in mistletoe. He has published a wide variety of articles. He has been involved in both sides, alternative and conventional, as well as research. We're very honored to have him here to speak to us today.

This is a very exciting field. I was very fortunate to get started in tumor immunology at Sloan-Kettering when it was in a tiny room the size of a large bathroom with Lloyd Old at the head of it 35 years ago. We're beginning to see the point where this is really coming into active use. For many years it was talked about. There's been a logarithmic growth of the literature on tumor immunology and the basic science behind it. I do want to say that the NIH – there really has been a lot of good basic work done for years and years, but we may not have seen the kind of results that we wanted to in terms of the war on cancer. Dr. Beuth.

Dr. Beuth: Thank you very much for the kind introduction. I was asked to give a brief summary of our experimental and clinical evaluation of the mistletoe lectin. We are a university group in Cologne in Germany, and we have been working on it for about ten years now.

Before I go into the mistletoe, I want to draw your attention to where this kind of therapy stands in oncology, or where we put it, where we situate it. It's part of the so-called scientific complementary oncology in Germany. This complementary medicine is not an alternative to standard therapy but a completion. I'm very glad that this morning the same opinion was expressed by several speakers. It cannot compensate the tumor destructive therapies or strategies, but it can complete them. What is very important for us is that we need an indication. That means we just do it on indication.

I've put on this slide a few of the so-called scientific complementary therapy options that we are testing in Germany. We have put all these treatment options under scientific evaluation. I'm pretty sure that we will have quite a few results in a couple of months and years. On the next slide I've summarized the studies that we are currently performing with the German Society of Oncology. Here's the mistletoe lectin we are doing in colorectal cancer, breast cancer and some other tumor entities. Beside the mistletoe, we have a big study in thymic peptides and enzyme treatment and antioxidant treatment, in tumor vaccination, in lectin blocking. I will talk about this on Sunday morning. What is very important is that all of this is under the auspices of the German Society of Oncology. All these studies are accepted by the German authorities. That means if they are successful, then we can apply these treatment modalities in our German clinics.

Now let's go to the mistletoe. I don't know whether you're familiar with this plant. It's a plant growing on trees in Europe. It was introduced in 1920 into the anthroposophical tumor therapy oncology. Ever since, it was disputed and rejected. It was rejected because the scientific evaluation was lacking of this treatment option. 1989 was a very dramatic point, because two

German scientists isolated the immunoactive component, the mistletoe lectin 1, out of the clinically approved mistletoe preparation.

We started the same year with a lot of pre-clinical evaluation of this substance. As soon as 1992 we started prospectively randomized clinical studies on the mistletoe lectin 1. One-and-a-half years ago, the first recombinant mistletoe lectin was introduced into the experimental immunology. Currently we are evaluating this recombinant mistletoe lectin. This might have a big future.

I have used the word lectin. What is a lectin? Lectins are carbohydrate-binding molecules. Normally they are proteins, glycoproteins. They are well-known in nature, for instance in brain tumor cells or in tumor cells in microorganisms. We did a lot of experimental studies on this, and in certain plants, for instance in the mistletoe. The mistletoe lectin is quite good characterized. It must be good characterized because otherwise we wouldn't be able to create a recombinant or express the recombinant mistletoe lectin. That means we know the genome. Here is an analysis of the structure. It contains two chains. It's the A chain of the mistletoe lectin which is cytotoxic. The so-called B chain has the lectin activity – that means the binding capacity to the receptors.

With this mistletoe lectin we did quite a lot of experimental work in the University of Cologne. I have just summarized it here. I will briefly start with the *in vitro* experiments, because we are forced in Germany to do the *in vitro* experiments before we go into experimental animals and before we go into patients. We could see important activation of certain immune cells, for instance of lymphocytes and of macrophages. We could see activation marker expression. We could see cytokine secretion.

What was very important in these *in vitro* assays was that we didn't see any proliferation of tumor cells under very low concentrations of the mistletoe lectin. This was obligate for our further studies. If tumor cells would proliferate, this substance would not be appropriate for treatment in human oncology. Another thing was very interesting. We found a dose-dependent cytotoxic effect, but not only on tumor cells, which can be taken from the literature. We found the cytotoxic effect against various tumor cells and against immune cells as well. That means it's nonspecific cytotoxic but dose-dependent.

After these *in vitro* experiments we did a lot of experiments in the murine system – that means in experimental mice. I can summarize this as well. Here again we could see a great activation of immune cells. We could see a special effect on thymocyte proliferation, maturation, and emigration into the peripheral blood. This was very interesting. We could see significant immunoprotection under steroid, under cytostatic drugs. We had a significant antimetastatic effect. We had a significant antitumor effect. We had a significant improvement of survival in experimental animals. For human use it was very important that we had no histologic organ alterations after long-term application of the mistletoe. That means it's quite safe to apply this kind of therapy even in human oncology.

The two experiments that I want to show you were done in BALB/c-mice. These are immunologically very well characterized mice. We applied two tumor models. The sarcoma L1 tumor goes after intravenous inoculation into the lung. It gives lung colonization or experimental metastasis in this organ. The RAW lymphosarcoma goes into the liver. The control group, which had application of non-immunogenic buffer, had a huge amount of lung and liver metastases after two weeks.

We treated the treatment group, or the therapy group, with the mistletoe lectin 1 in the optimal concentration that was established before we did these experimental designs. We applied it twice a week subcutaneously over two weeks, and we had a dramatic reduction in lung and in liver metastases. That means in these experimental models we can induce a very potent antimetastatic effect by the immunomodulation with this mistletoe lectin. Reduction of metastases is not the key point. We wanted to see whether the mice actually are protected from this treatment. Do they survive longer? Is there any benefit for their survival?

It's the L1 sarcoma which goes into the lung. We had applied two concentrations of the mistletoe lectin. I have put into this figure the highest concentration that was working and the lowest concentration that was working, so we made a big concentration kinetics. Here is the control group, which had the non-immunogenic buffer. To summarize, after 24 days, 90% of the animals in the control group were dead, whereas in the experimental group we had more than 80% survivors. That means we had great effect on the overall survival in this experimental model. We had three other models tested in the same way. The results are very similar. We are currently doing these experimental tests on the recombinant mistletoe lectin. This is as potent as the native mistletoe lectin was.

I want to turn now to the human therapy. We had a consensus in 1969 within German immunologists on how to treat oncologic patients with the mistletoe lectin or with the standardized extract, which was standardized on this immunoactive component. We always apply the optimal dose of the mistletoe lectin, which is one nanogram per kilogram body weight. We give it subcutaneously twice a week, just like we did it in the experimental models. We do three months of therapy followed by a two to three month break, and then again therapeutic application for three months. We found that this break is very important. After finishing this

break and going into the therapy again we could boost the immune system. At least white counts and activities of peripheral blood cells were upregulated higher afterwards, so this is to induce this booster effect.

We didn't see any evident side effects. Sometimes we have on the injection site a mild granuloma formation. We have a reddening, sometimes an edema. Since our patients were all tumor patients, after tumor destructive therapy the immune system was so suppressed that we didn't expect these locally induced side effects. There were no immune cells, or not enough immune cells, in the peripheral blood to induce these side effects. We did not see any systemic side effects, but we didn't go higher into the dosage. If we go into a higher concentration, we might have systemic side effects as well.

What could we see in our first application in the patients? It is important to remember that all these data are under non-study conditions. That means we treated about 200 patients with the mistletoe lectin and evaluated the immune parameters. We could see again a great activation and a great upregulation of peripheral blood immune cells. We could see an acute phase reaction in the peripheral blood, which obviously is cytokine-induced.

What is very important – we saw a great endorphin upregulation. I don't know whether you're familiar with these. These are endogenous morphine-like substances which have an influence on the mood of the patients and on the pain perception. These endorphins correlate very well with the quality of life that we evaluated in the different questionnaires. I want to show you how it is possible to measure these endorphins.

These were breast cancer patients, 50. It was a randomized trial. We divided them into a control group and a treatment group. These were advanced breast cancer patients getting an established chemotherapy regime in Germany. In the control group the beta endorphins are very

stable during twelve weeks of measurement, whereas in the ML1 treated group we had a great increase after six weeks. This increase was stable as long as we injected the mistletoe lectin. Interestingly, these increased levels of beta endorphins correlated very well with the quality of life that we measured in different questionnaires.

We were forced in Germany to introduce or to do prospectively randomized clinical trials, and we started them. I have the tumor entities here – ear, nose and throat carcinomas, breast carcinomas. We started with university clinics in Germany. They were very open when we started, when we presented our data. They immediately agreed to do these studies. Nowadays the German hospitals are a bit more open, so we have more partners in Germany right now. But it's very interesting that the university clinics were our first partners.

I just want to show you two or three studies. One study was on colorectal cancer patients Dukes D – that's an advanced stage of this disease. After looking at the inclusion and exclusion criteria, we randomized into a group which got an established or standardized chemotherapy option and group B, the treatment group, which got additionally the optimal dosage of the mistletoe lectin. We had in six-week intervals a follow-up of diverse parameters of the peripheral blood, and of the quality of life.

Our prime criterion was the quality of life, and we had several secondary criteria which I will show you. We measured the quality of life with a very popular questionnaire in Germany, which is very sensible because it has a high score range. It's effective as a functional assessment of cancer therapy. I've put the components which I tested here on this slide. It has a score of 200 with the optimal score of well-being in the highest score range.

I want to draw your attention to these few numbers here. The significance is that between the two arms there's no difference until week 12. As soon as week 12 we had a

significant increase in quality of life in arm B, the group which had additionally the mistletoe lectin. That means after some time of treatment we can measure it in these defined questionnaires. Interestingly, this correlated again very well to the beta endorphin plasma levels.

The other criteria that we evaluated – what did we see? We saw significant increase in mucositis, great in duration. Mucositis is very suppressive for the patients, so this gives a better quality of life. We had a significantly decreased leukopenia – that means immunoprotection in these patients. We didn't see any influence on the remission rate and on the remission duration. We didn't see any influence on relapse-free interval and on the overall survival. Maybe the tumor stage was not appropriate for these criteria, so we are now testing in other tumor stages.

We did another prospectively randomized clinical trial with glioblastoma. These were about 100 patients, just the study design. Before surgery we looked at the immune system and we checked the quality of life. The patients were operated and had a corticosteroid prophylaxis for edema. After surgery we started in the therapy group on day one with the mistletoe injections and checked regularly the quality of life and the immune function of the patients.

To summarize it, what did we see? We saw significant decrease of peripheral blood cell counts and activities under the tumor destruction. This was very obvious, because all the patients received steroid prophylaxis as well. But in the therapy group, which was treated with the mistletoe lectin, we had after six and twelve weeks significantly increased counts and activities of peripheral blood cells as compared to the control group. We also had a significantly increased quality of life, which was measured by the Spitzer questionnaire in this case. Here again we could see a remarkable result.

Let me summarize. Can we recommend such a treatment for oncology patients except in clinical study? We in Cologne think we can, because we saw in our studies evident

immunoactivity which can be induced by this substance. We saw an improvement of quality of life. And we could measure immunoprotection under tumor destructive therapies. This all was measured in prospectively randomized clinical trials, so it's rather stable.

What we want to see, and we didn't evaluate until now (it's under investigation currently), is whether we can reduce tumor relapse and metastasis rate by this treatment and whether we can prolong the overall survival. I want to give a warning, and I'm very happy that I heard the same warning this morning from my American colleagues. I want to summarize it: Mandatory for optimizing treatment modalities from conventional and complementary medicine is the restriction to therapies with scientifically evaluable and reproducible benefit for the patients. This is very important. We should not focus too strongly on single cases. We need studies and we need a reproducible benefit for the patient. We also need, and I heard it this morning as well, standardized documentation and a scientific evaluation. If you are interested I invite you all to do it with us. I think it's possible even across the Atlantic. Thank you very much.

Dr. Dattner: Thank you very much, Dr. Beuth. Our next speaker is Dr. Ralf Kleef. He did his university studies at the University of Witten-Herdecke in Germany, a school that has an anthroposophic orientation. He did his residency with Dr. Dieter Hager in Germany at the largest cancer clinic in Germany, and did postdoctoral work at Sloan-Kettering with Lloyd Old who I had studied with years before. His work there was in psychoneuroimmunology as well as in proteolytic enzymes. He was later chosen to be an Office of Alternative Medicine advisor on Coley's toxin, which I believe he's going to speak about today. His work now is at the University of Vienna where he is studying and using hyperthermia. I introduce Dr. Kleef.

Dr. Kleef: Thank you very much, Alan. Ladies and gentlemen, I'm very happy to be here today. Alan just mentioned Lloyd Old. Lloyd Old's group is the group at Sloan-Kettering which in 1975 discovered TNF, which we call tumor necrosis factor. This is a group which actually raised a lot of hope in the scientific and lay public domain when tumor necrosis factor was first identified as a factor which induces tumor necrosis.

Lloyd once told me there is no alternative medicine or mainstream. There's either good medicine or bad medicine. I believe that we are moving into a very fascinating time in medicine. I regard this conference as one of the milestones in the field, because up to now there was an unfavorable bias to mainstream medicine. We now move more along to funding proper scientific research which looks into a wide realm of mind-body approaches, immunologic approaches.

My topic today is fever and cancer. This is one of the most fascinating topics in the whole field of cancer. Let me tell you the two major parts of evidence which make this is so interesting. We know there is an extremely strong correlation between a missing history of fever in the history of cancer patients. This refers to childhood fever and fever in adulthood and the incidence of a whole variety of epithelial cancers and also of hematological malignancies. This is very strong evidence, and in my concluding remarks I will tell you what I think we should do with this evidence.

The second strong piece of evidence for the relation between fever and cancer brings me to Dr. William Coley. He observed a patient who underwent a severe infection of the skin, an erysipelas infection which brought him into a very high fever which lasted for many days. This patient experienced a full regression of a huge head and neck cancer. This brought Coley to the

idea to identify bacteria and heat inactivate them and inject them into cancer patients. This turned out to be what we know nowadays as fever therapy.

The history behind that is huge. We would need to spend a whole week discussing the mechanisms of action, how this works. I'm trying to walk you very briefly through it. What can be taken from it is that this is an ingenious approach to try to mimic the body's own defense system against cancer. The epidemiological data are hard, good data, which are available. I can provide them to anybody who is interested in this literature. From the data we know that if we induce what we call artificial fever there's a good stand for expecting tumor regressions.

What actually do we know? We know a lot and we know not enough. I spent exactly one year at the Office of Alternative Medicine and in the time afterwards to try to get together the evidence for this rationale. The more I learned, the less I knew. We can sort the picture out, I think. This is William Coley at the height of his career and his daughter Helen Coley Nauts. When I was invited by Wayne Jonas to review this evidence at the Office of Alternative Medicine, we experienced one of the biggest problems in analyzing data. When we tried to compare patients off the National Cancer Registry, the SEERS database, with Coley's and tried to pair match those patients, we tried to be very strict. We subtracted all additional treatments the patients had received during Coley's time.

We know this is not a fair trial for Coley, because we do know that to treat cancer we need multi-disciplinary approaches. We talk about mind-body medicine. We talk about a lot of immunotherapies. We talk about chemotherapy and surgery. All of those have to be taken into account. I'm going to show you a preliminary analysis of the group at M.D. Anderson who did work with this, Mary Ann Richardson's group. Still, if we took only the Coley treatment, nothing else, the patients treated 90 years ago, at the turn of the century, achieved the same

results as the best medical care of today in the 1980's from the registry of the National Cancer Institute. This already is quite a strong statement.

This is an abbreviated documentary of the history of Coley toxins. It was German doctors who initiated these therapies in the beginning. This is 1868 and this is where Coley initiated this at the end of the last century. This is Coley's active career from 1890 to 1936, and you see all these vaccine developments stand here. Here is this discovery in 1975 of Carswell. This is Lloyd Old's group at Sloan-Kettering which discovered TNF, and it has been going on and on since.

We know that from the beginning of the discovery of interferons, interleukins and tumor necrosis factors, this is not the solution of the cancer problem, because we are dealing with a highly complex immunological system. To try to put into it just one cytokine, one of those hormones of the immune system, doesn't solve the problem, unfortunately. So it has been a long-standing history.

What Coley actually did was induce artificial sepsis. Artificial sepsis is something you shouldn't fool around with, because it can kill patients. Coley lost patients. We know during this last century doctors inevitably killed patients by inducing this artificial sepsis. We are dealing with something not very easy to deal with and not very pleasant. High fever induction over a prolonged period of time takes much from the patient.

These are just some of the cytokines we know are being induced. Let me mention interleukin-1, interleukin-6, TNF, but one of the most promising and probably most important cytokines to study is interleukin-12. For those of you who are immunologists, interleukin-12 actually is able to switch T helper 1 to T helper 2 cells and vice versa. This is the cytokine which regulates the expression of T helper 1 and 2 cells.

In a cancer patient, to make it very simple, we would wish a T helper 1 response which are proinflammatory cytokines. In a patient who has a chronic autoimmune disease, we would like to induce a T helper 2 response because we know these cytokines are immunosuppressive. In a cancer patient it's unfortunately often exactly the opposite. We do find a high level of T helper 2 cytokines being expressed, and this is the rationale where Coley toxins come in. These are other landmarks of the history of tumor immunology.

I delivered this therapy to a couple of hundred cancer patients. When I talked to them about what we were going to do, I explained the following: Imagine we throw in your body a signal, and this signal shall activate your immune system. Let's imagine this signal is a heat-inactivated bacterium. We have all those lymphocytes crawling around the body. Now imagine. This is the bloodstream, and this is the place where you want your white blood cells. When we measure blood cells in the bloodstream, it is not the real-world model. We just measure quantitatively blood cells.

What is really important and interesting is what's going on outside in the tissue where we find our tumors. What's happening is that these cells are being activated. All those lymphocytes extravasate. They leave the vessels through tiny junctions and they go for this heat-inactivated bacterium. That is what is needed. They need to extravasate. This picture shows how our white blood cells are formable and what they actually can do.

This is what I wanted to cover. These are the so-called cell adhesion molecules. Cell adhesion molecules are among the most fascinating molecules governing the cellular and tumor immune response, because these are molecules on the surface of lymphocytes, and also on the inner lining of the blood vessel. This is the inner lining. We do know nowadays that those cell

adhesion molecules are being activated, which enables these cells to extravasate. We have studied that extensively at Sloan-Kettering.

You see how a cell actually leaves the bloodstream and goes into a tissue. This is not a white blood cell. It's an erythrocyte, but it holds true for lymphocytes as well. Now you have this highly activated immune system, and the cells think, "Oh, my God. Here is a severe streptococcal infection taking place." But we fool the immune system, because this streptococcus is inactivated. All these blood cells are activated. Then suddenly one of those lymphocytes says, "Hey, now we are all out there, but I actually see a cancer cell over there. Why don't we go for this cancer cell?" This is a very simplified model of how we can understand fever therapy. The picture is very complex.

One thing we do know is that we do need an immunological preactivation. What do I mean by preactivation? Look at the historical picture. Here we have the tuberculosis death rate per 100,000 in the population in 1890, the beginning of Coley's career. And here you have the cases cured by Coley's vaccines. You see Coley is getting less and less and less successful towards the end of his career. This was a very fine physician who of course tried to refine his techniques, but he was less successful.

I am allowed to reproduce this picture from Charles Starnes at Amgem in California, who was probably one of the most renowned specialists on Coley toxin. He should be here instead of me today. It was Starnes' suggestion that the preactivation of large parts of the population with tuberculosis actually enabled the Coley toxin to work better. What does it mean for immunotherapy today? It means we know we need to preactivate the patient. We have heard a lot about mind-body medicine. Ladies and gentlemen, this is a strong preactivation. We've

really got to work with the patient and get him full into action, including his will to survive and his compliance with any treatment.

TNF was discovered in a BCG primed mouse. This means the mouse was activated with BCG (the agent which induces tuberculosis), and then they actually found the tumor necrosis factor. This is the most important phenomenon happening when we talk about fever therapy. It's called the Shwartzman phenomenon. This was done in 1936. Shwartzman actually injected LPS. LPS is lipopolysaccharide from gramnegative bacteria, one of the most important components of the Coley toxin. He injected it systemically. Twenty-four hours later he injected it systemically again, and the animal died. This means there was a sensitization of the animal.

Here comes the important thing. When he injected it localized in the skin and he injected 24 hours later systemically, he observed there was a necrosis at the prior place of local injection. This is exactly what's happening with the tumor. This is what it looks like when you inject LPS locally and 24 hours later you inject it systemically. You find a necrosis at the place of prior injection. The interesting thing is that this Shwartzman phenomenon, for reasons we know have to do mainly with TNF, takes place when we do this in a cancer patient, in tumors. If we presensitize a patient and subject him to LPS systemically, the necrosis takes part in tumors only. This also works if we give it interperitoneally. We don't have to give it systemically only. This is one of the most important findings. This has been learned since 1936. It's really surprising science has forgotten this.

This is a picture of how they showed that TNF actually works. I'm going to skip that basic test for the mechanism. This is another important thing, but I have to skip that as well. This is the action of endotoxins, how they actually accumulate in the body. If we give external exotoxins, pyrogenic exotoxins, we inhibit the ability of the liver to clear endogenous endotoxin.

By this translocation pathway we increase the endogenous endotoxin levels which again leads to this unspecific immunostimulation. These are the phases of the immune response. We know the macrophage is in the center of our interest.

Beneficial effects are moderate fever, a generalized stimulation of the immune system, and microbial killing. Harmful effects are very high fever, hypertension, disseminated coagulation and lethal shock, so this is a treatment we have to be very careful about. Fever is a highly complex phenomenon. As I said in the beginning, we need a week to talk about the whole mechanism. All these cytokines being induced induce a whole spectrum of immunological reactions which are impossible to cover.

TNF and interleukin-1 are the two most important ones, and I mentioned interleukin-12. The expression of MHC complexes are very important. These are lymphocytes attacking a tumor cell, all those small white ones. I have to quickly show you this. This is very important, because if you establish a tumor mass in a mouse there is a certain period of time which needs to pass for the immune system to develop a response. Here we have the window in time. If we catch the patient in that window of time and immunize him, there is no tumor growth. If we wait too long the tumor becomes too big; it's too late. This is why surgery still has its important place in tumor debulking.

This is a summary of all this. This could go on for pages and pages. It's very complex. Coley in 1935 quoted, "I will call attention to one cytokine to anyone familiar with the history of medical discoveries. The relative value of such discoveries bears not the slightest relation to the rapidity of acceptance by the medical profession." Ladies and gentlemen, even 100 years after Coley initiated it, we have an urgent need for further research in which bacteria we should take.

This is a big task, and the big problem is money. You can't patent this easily because it has been around for such a long time. Helen Coley Nauts and I went to Pharmacia in Sweden three years ago. They said, "Show us the way how to patent it. We believe that this works. If you tell us how to patent it, we will give you the money." I'm very grateful to Dr. Wayne Jonas that he showed interest in this topic, because I think Coley can be named with all respect the father of immunotherapy. Thank you very much.

Dr. Dattner: Thank you very much, Ralf, for that lightning-fast enlightening talk. There's so much information here that we may have to run a little bit over.

Without further ado I want to introduce Dr. James McCoy who is now director of research and clinical testing at the Immunocomp Laboratory. Previously he was the director of ImmunoQuest Laboratories in Gaithersburg, Maryland. From 1976 through 1982 he was a cancer immunologist at the NCI, when I was down there. We didn't know each other. With 10,000 people there it was a little hard to know who was who. He's been very involved with a number of things. He has a huge list of publications, and many other honors to go with it. I want to get him up here rather than his honors, so let's hear his talk.

Dr. McCoy: Thank you. A lot of the work that has been presented this afternoon is very fascinating to me, because the bottom line is how to use the immunologic system to cure a cancer patient of a rapidly or slowly growing metastatic tumor. When I was at the NCI, I had the fortune of working with a good group of scientists whose focus was immunology. We were interested in determining whether the host, the tumor-bearing host, could indeed recognize

cancer cells as intruders and then in some fashion figure out how to kill those cells immunologically.

There are a lot of tumor models that have been developed where we could literally cure animals of their cancer disease by immunologically manipulating the host. I studied many of those myself. It's very simple to do in animal models. But when you get into humans it is much more difficult. A lot of the early work of what I'm going to talk about today has been done many years ago. A lot of the principles remain the same.

My focus has been attempting to use immunology textbook hypotheses and proven mechanisms of how the immune system works to develop a formulation that will indeed specifically allow the host to be immunized against his or her own tumor, so that the immune system can kill the tumor. The nice thing about theoretically doing that, or doing that indeed, is that there are no toxicities associated with this kind of therapy. I'm going to present data today on over 500 cancer patients who we had immunized with the procedures that I'm going to discuss. We have indeed seen, if anything, very mild toxicities, and in most cases no toxicities.

I want to emphasize, as has been pointed out earlier today, that the quality of life is, if anything, enhanced by our treatment. This is really important to a cancer patient and a cancer patient's family. Ninety-eight percent of the patients we have treated have witnessed an enhanced or an improved quality of life. This of course is very divergent from traditional therapies that are highly toxic, as we all know.

These are various areas where the immune system sits in the body. Normal cells of the body look normal to the immune system of the body. A cancer cell has little spikes on the outside of the cell membrane. The point is that cancer cells are foreign to our bodies. That's been shown by many different investigators worldwide.

As pointed out earlier, the actual development of immunotherapy was over 100 years ago for cancer. Through the last 20 or 30 years most of the emphasis on immunotherapy has taken place. Several things have been shown. For immunotherapy to work in a cancer patient, the cancer cells must possess tumor-associated antigens. The tumor-associated antigens must be immunogenic. In other words, they must be able to make the host respond against them. They must be free of blocking factors. In other words, if there's something covering up these tumor antigens, even though the immune system may be activated, it's not going to be able to reach in and kill those cancer cells.

This is a very fascinating area. It's out of my realm, but I do believe that blocking factors occur in cancer patients, and that's the reason we have nonresponders in many cases. The question is how to remove those blocking factors in a nontoxic, effective manner. I don't know that answer.

The other point is that the cancer patient's tumor load cannot be overwhelming. We know from our experience that it's very difficult, almost impossible, to immunize a patient who has a large tumor burden. A large tumor burden is quantitatively difficult for the immune system to handle. Also there's enormous debilitation that occurs in an advanced cancer patient, physiologically, immunologically, great deterioration. It's very difficult to get anything to work. We have had some miraculous successes in some advanced cancer patients who literally we did not think we could do anything for. One never gives up. Yet one has to realize that the larger the tumor burden, the more difficult it is to treat a patient.

The immunotherapy studies to date that are published in peer-reviewed journals and non-published make clear a lot of factors. One was pointed out by the previous speakers. If you have

an existing immune response against the tumor – in other words, if the patient already has some sort of immune response against the cancer – it’s much easier to get immunotherapy to work.

Second, the thought is that we’re going to need some kind of a combination treatment. I’ve been intrigued for a long time with Coley toxins, as to how it’s working and the fact that it’s quite obviously working. But it may be only one factor of many that we need to put together in an immunotherapeutic formulation to get the real job done – curing the patient of the cancer. We’re using a combination treatment.

The data shows that intense treatments can lead to adverse side effects. We customize our treatment to each given patient. We’re optimizing these patients so we know we’re not dealing with toxic levels of the immune-stimulating agents that we use. These theories were put forth by Adi Kedar and Eva Klein in *Advances in Cancer Research* in the early 90’s. It’s not something that I came up with.

Immunocomp is the name of our clinic and laboratory. Patients come to Atlanta, Georgia, and we treat them there. We customize the treatment to each patient. The thrust behind our treatment is to attempt to develop cytotoxic T killer lymphocytes specifically directed and educated to find tumor cells that have those spikes, those tumor antigens on them, and kill them. I want to again emphasize that if one can do this appropriately and properly, there’s no toxicity involved. The patient is not going to be debilitated, or go through “hell.” This is an actual picture of a cytotoxic T lymphocyte attack, which is the little green cells attacking tumor cells. This is an electron microscope picture. It’s quite dramatic and pictorial. This has been shown over and over again in various laboratories. We have treated over 500 cancer patients in our study.

I want to emphasize that the reason we can reach out into the public today and actually treat cancer patients, whereas a lot of other centers cannot, is that we're fitting within all FDA regulations and guidelines. We've had a very extensive FDA audit. Basically we're using two FDA-approved drug agents. One is interleukin-2. The other is granulocyte-macrophage colony stimulating factor. These are both approved by the Food and Drug Administration. In our formulation we're using these two agents at low, nontoxic doses. We're also immunizing the patient with the spikes, those tumor antigens, from their own tumor cells. So we're giving nothing foreign back to the patient, as well as we're using FDA-approved drug agents. We don't have to go through exhaustive IND clearances from the FDA to offer this treatment today.

Of these 500 patients, we have been able to evaluate 350. We have enough time, at least a year of treatment time, to be able to make some statements about whether we feel we're getting responses or not. We've been doing this treatment for four-and-a-half years. We've done it very methodically, very scientifically, very carefully. That's the reason we've only treated 500 patients today. We want to make sure this is done in the most scientifically, medically sound ways possible.

Most of these patients were far advanced. Traditional therapies had been exhausted. They had failed from chemotherapy, radiotherapy treatments. At the date of this analysis, 84 of the 350 patients, or 24% of the patients, had shown significant clinical benefits from this treatment. I define that as complete remission, or at least 50% partial remission of tumor, or six months or greater stabilization of disease, where there was no disease progression. This is verified by pre- and post-treatment CAT scans, bone scans and tumor marker analysis. This is a slide of the protocol.

Almost every human tumor that has been studied appropriately today has been shown to be antigenic or to have tumor antigens. Therefore, immunotherapy treatment for cancer today or in the future should theoretically work in every type of cancer.

The specific approach we use is to customize this treatment to each patient. We get a blood specimen from the patient to begin with. We separate the blood mononuclear cells from the whole blood of the patient. We add different concentrations of IL-2 and GM-CSF into the patient's mononuclear cells. We get a dose response in terms of stimulation of the mononuclear cells of the patient, so that we know the optimum level to give a patient. We also know to stay away from doses that are going to show toxicity. This way we can keep the patient very targeted, using doses that are going to be effective yet not toxic.

We re-verify this every four to six weeks through continuous testing of the patients. We're constantly adjusting the immunotherapy formulation for the patient as the patient progresses with treatment. We have to get a biopsy from the patient. This has to be a fresh biopsy basically, or a frozen biopsy. We have a method of pulling the tumor antigens very gently off of the cell membranes of these cells. This is a hypotonic saline membrane extraction procedure. It was originally developed in England on mouse lymphocytes and later developed by Ron Herberman, who I worked with at the NCI with human tumors.

Now that we have the patient's own tumor antigen, we know the concentrations of IL-2 and GM-CSF that are optimal to that patient's immune system. We immunize that patient, or inject that patient intradermally, with each of these agents. We give the shots in the groin area, very close to the inguinal nodes. We give the tumor antigen one to two inches below that area. We give the GM-CSF in that same area. We give the IL-2 shots intradermally right over top of

the lymph node bed. We do this because there are several publications in the mouse tumor model literature showing this is the way to optimally immunize a mouse against tumor.

The tumor antigen goes in. As was discussed earlier, we're actually fooling the immune system. The immune system thinks that the patient has cancer right here, because we're giving the footprint of the cancer cell, the tumor antigens. We're now giving GM-CSF at that same location. We're asking that macrophages drain out of the lymph nodes. Once they figure out that there's a foreign intruder there (that is the footprint of the tumor itself, the tumor antigen), the macrophages migrate into that area. They are activated by GM-CSF. They then travel back to the lymph nodes, where they give the message to the T lymphocyte to become sensitized to the tumor antigen. The IL-2 causes a proliferation of these cells that by definition have become cytotoxic T lymphocytes.

The bottom line is that we have used the basic principles of immunology to explode the immune system against the cancer in a nontoxic fashion. This slide shows the pretreatment, the lymphocyte immunity in patients prior to immunizing them, versus their reactivity after we immunize. It shows that we can greatly further activate the immune system against the tumor antigens. We have shown that 70% of the breast cancer patients and 80% of the melanoma patients prior to even immunizing them have some existing immunity against their tumor antigens. The level of immunity is low. As we start immunizing them, it markedly increases. We're immunologically monitoring these patients as we immunize them to see what drives their immune reactivity, specifically against their tumor antigens.

Here's a set of data with non-Hodgkin's lymphoma patients. This data set has increased more than nine patients since we tabulated this data. Total clinical successes in non-Hodgkin's lymphoma patients are six out of nine at this point in time. Can it actually be really true? It

actually is really true. There are only eight melanoma patients, but five out of these eight patients have shown clinical responses. Melanoma is a tumor type that responds to immunotherapy, even more general nonspecific immunotherapy. It's not surprising that we're seeing what we are with melanoma patients.

The largest set of data we have today is with breast cancer patients, who have consistently failed to respond to immunotherapy in the past, except in some anecdotal cases. There were some with Coley's toxins that did respond. Most of these patients are at least two years out. Some of them are four-and-a-half years out. The point is that we have a 44.8 response rate in breast cancer patients. These are mostly patients with advanced disease. When these advanced patients are treated with the left over neutron bombs of chemotherapy – taxol, Adriamycin, whatever – usually you get about a 5 to 7% response rate in these patients, compared to our response rate. It's actually not 44.8. You're going to see in the next slide what it really is.

This is our breast cancer patients' response in stages III and IV. Here are the stage IV patients with about 5 to 7% response rate with conventional therapies. There's a lot of toxicity. Here we're seeing a 23.4 % response rate. Many of these patients are totally tumor-free. Chemotherapy does not cure a breast cancer patient. It delays death, basically, with a lot of toxicity.

When the tumor burden is less, for example with stage III patients (we only have ten of those patients today), we have had seven out of ten clinical responses in those patients. With stage II patients, seven out of eight patients. None of the stage I patients, who really had no evidence of disease at the time we immunized them, have relapsed. The point of this chart is

that, even though these data are somewhat preliminary, the less the tumor burden, the greater the chance of immunotherapy success.

Other tumor types are showing some responses – colon, lung, ovarian, prostate. The point I want to make again is that there's no clinical toxicity associated with this. If there is any, we have seen some mild nausea, generally within four to 24 hours. It leaves within 24 hours of treatment. This compares our treatment with conventional treatment. This shows the difference in our treatment versus other immunological approaches. A lot of those approaches try to sensitize and stimulate the immune system in a general way in the patient. We're trying to specifically sensitize against tumor antigen and to generally stimulate with IL-2 and GM-CSF.

I didn't mention many of the groups in Europe that have a large dedication and emphasis on immunotherapy. Within the United States, a large number of groups are attempting to develop immunotherapy treatment. It is the wave of the future. Again, the difference between ours and others that they're trying to develop is specific sensitization against tumor antigens. We're within FDA guidelines, and many of these are not. They are going to have to take exhaustive IND procedures. A lot of these approaches which are either very similar to ours or may end up as good as or superior to ours are going to take years to reach the public. We can reach the public today. Why is our treatment more successful than most? Because we're customizing to the patient. We're using textbook procedures.

I have to wind it up, and that is it. I thank you for your time.

Dr. Dattner: I want to thank Dr. McCoy for that very impressive presentation. Certainly this is a very exciting aspect of tumor immunotherapy, to get right down to using the specific antigens. Of course, we have all the problems of antigenic drift and covering up the molecules.

We can see the excitement that might be generated by using potential removers of the things which cover those antigenic sites, like the use of high dose enzymes, if that is actually uncovering some sites. There are many different things which might be combined with it, reducing tumor antigen circulation, possibly by some of the “cleansing” therapies. One could imagine many exciting things that might combine from the alternative world with this.

Dr. Jeffrey White, who is at the NIH, is going to make some comments, ask some questions of the presenters and give us further perspective on the work that’s been presented so far.

Dr. White: Thank you, Dr. Dattner. I didn’t prepare specific comments about individual talks. I know there are a number of questions and that we’re running over. I’m going to open up with a single question for each person still on the panel. Dr. Freeman has left already. Then I’ll let you get to the other questions that you’ve had.

Ralf, I’m interested in what you think the mechanism is for Coley. Do you think it’s the same as for the Shwartzman phenomenon, or are there some differences between the two reactions?

Dr. Kleef: Jeffrey’s question was whether the Shwartzman phenomenon, which is the necrosis of tumors, is the basic mechanism of tumor regression in Coley. The answer is no, because the Shwartzman phenomenon always leaves a ring of viable cells in the periphery of the tumor. The larger the tumor, the more likely you are to have this ring of viable cells at the periphery of the tumors. The Shwartzman phenomenon is only a simple hemorrhagic necrosis which actually works on the very fragile microvasculature of the tumors.

Coley toxin does induce the Shwartzman phenomenon, and that's a very important mechanism. But what comes into account as well is the activation of the whole cytokine cascade. We could talk for weeks about that. This is a piece of work which contains 1,273 scientific references on the mechanism of action. We actually should spend a whole conference on that. But we know that it is the regulation of the whole cytokine cascade which eventually led to the dramatic full remissions Coley observed mainly in sarcoma patients.

Dr. White: One other question for you, Ralf. Do you think it's known now what the proper way is to standardize endotoxin and exotoxin, or is there still more work to be done in that area?

Dr. Kleef: The group at Sloan-Kettering has done that over the last year. They have identified which bacteria, grampositive and gramnegative bacteria, induce which cytokine profile. Surprisingly, these results are not published. This is the first personal communication by Helen Coley Nauts, who was in close contact. In my opinion, we know this. We know that the strains Coley used which are available from the American Tissue Culture Collection are much more powerful than newer bacteria. The content of endotoxin differs from those old stems to those newer stems up in the order of 3 magnitude. All these things have to be taken into account.

To answer your question, we do know optimal procedures to produce a Coley toxin close to what Coley used. What is more, nowadays we could actually investigate precisely which cytokines are being induced in which time span. It could be done, but nobody puts out the money for it. The Cancer Research Institute, which has been pioneering the field, is not up to

doing this. They are very much into tumor antigens and heat shock proteins, which are very important tasks, but nobody is going to do this mixture. To them it's obviously not feasible enough, which is very sad.

Dr. White: Thank you, Ralf. A couple of questions for Dr. Beuth. Your animal studies with the mistletoe lectin were with the lectin alone and showed decreased numbers of metastases in the two models. In your patient studies you're using it in combination with chemotherapy. What do you think the potential interactions are between those two?

Dr. Beuth: Normally we don't use it together with chemotherapy. We use it after the chemotherapy. That means the patients come to us after they've finished their tumor-destructive therapy. Normally we don't treat the patients in combination with chemotherapy or radiotherapy and immunomodulation, but afterwards. In exceptions we do, but normally we don't. That means first they get their tumor destructive treatment, the complete treatment. Afterwards, we try to recompensate the immune system with an immunoactive component.

Dr. White: Do you see with any particular chemotherapies any decreased ability to improve immune function? Are there specific agents, for example, that give long-term damage to the immune system?

Dr. Beuth: We have quite a lot of experience. We looked at people under surgery and found that there's a great immunosuppression without any other modality – just caused by the surgery. We made a big study on radiotherapy. We know that after radiotherapy the lymphatic

system is decreased for years sometimes. That's a good target for immunotherapy. There are different modalities when you can elevate, upregulate and activate the lymphatic system, so that's a point. We have the experience that in certain chemotherapy regimes, lymphocytes and lymphatic cells are extremely suppressed, whereas in other chemotherapy regimes more the neutrophilic granulocytes are suppressed. They are targets as well. We look at the kind of chemotherapy. We look at the kind of tumor destruction. Then we decide what kind of immunotherapy we induce.

Dr. White: Have you tried any adjuvant approaches, post-surgical approaches in patients who have no evidence of gross disease? Have you used this in any patients with only micrometastatic disease or no detectable large tumors, for example adjuvant colon cancer or breast cancer?

Dr. Kleef: We've made a big study not on the mistletoe but on bacterial immunomodulators. We made a big study on bacterial immunomodulators where we stimulated the patients one time before surgery at a certain time in colorectal cancer. We included Dukes A to Dukes D, all the stages. In Dukes A and B we had the best results. That means in our experience, the earlier we can treat a tumor, or the less advanced it is, the better is the immunotherapy.

Dr. White: Thank you. A question for Dr. McCoy. With the patients you were showing us, for example the breast cancer patients, you mentioned that your group is doing combination

therapy. Do you mean that they get other modalities along with this therapy? What else is involved in that?

Dr. McCoy: What I meant by the combination is that we're combining the tumor antigen with IL-2 and GM-CSF. Most of the breast cancer patients had already received and completed chemotherapy and radiotherapy, so they were not on those protocols at the time of receiving our immunotherapy. They were on those protocols prior to receiving our immunotherapy.

Dr. White: When you do your cytotoxic T cell studies before and after therapy, how do you do those?

Dr. McCoy: We're starting those with Emory University today, the cytotoxic T lymphocyte studies. We're evaluating tumor antigen reactivity pre- and post-treatment with a lymphocyte blastogenesis assay that we developed at the Cancer Institute. We're basically taking the patient's blood mononuclear cells and stimulating those or interacting those cells with various doses of the membrane tumor antigens. We published a series of articles in the late 70's and 80's describing that technology.

Dr. White: So you're looking at proliferation of cells?

Dr. McCoy: We're looking at proliferation. The presumption is that we're turning on a cytotoxic T lymphocyte. That was the early slide I was trying to show, the mechanism of action

that we presume we're turning on. We have not fully demonstrated that in our studies. Again, we just started those studies with Emory University.

Dr. White: Those are the questions I had. We can get to the rest of the group's questions.

Dr. Dattner: Thank you very much, Dr. White. One question that came up for Dr. McCoy was on possible selection bias. We started with 524 patients and 350 of them were evaluated. That means there was a 30% dropout.

Dr. McCoy: Actually there's no dropout. We've only evaluated 350 because we've only had time under our belt with 350. The additional 150 have been on study for too short a period of time to evaluate. None have ever been dropped out.

Dr. Dattner: Thank you very much. Is this available? At what kind of cost?

Dr. McCoy: It's available today at a very nominal cost. We are covering our research and development costs and our continuing research costs. If you would like specifics on cost, please call our office. We'll be happy to go through those with anyone. The number is (770) 474-4422. It is available. We're not doing it on a widespread basis. We're trying to do this in a very systematic way so that we're collecting as much as we can. Yet we are offering it to patients.

Dr. Dattner: How much tissue do you need?

Dr. McCoy: We need fresh or frozen biopsies of the patient. We need at least two 18-gauge needle aspirates, biopsy aspirates, which is very minimal. These tumor antigens are highly potent in the way we're using them. We'd like to get a piece of surgically removed biopsy at least three millimeters in diameter or cubed, but we can get away with less than that. Certainly we'd like to get the patient's material at diagnosis.

Dr. Dattner: Do you treat glioblastoma, fibrosarcoma, and soft tissue sarcomas?

Dr. McCoy: We've had some success with sarcomas, specifically Ewing's sarcomas, less with chondrosarcomas and fibrosarcomas. We've had some success with leiomyosarcomas. With glioblastoma we've had no success. We've only treated three patients. These were Canadians. I certainly don't feel we had any success. We may have increased survival a few months in the patients, but it's very difficult for us. I certainly don't want to leave the impression that we can treat a glioma.

Dr. Dattner: How large a tumor gives a chance of a failure of the immune therapy?

Dr. McCoy: We have a series of physicians and scientists at Emory University who are going to help us evaluate all of our data, therefore taking my personal bias away. I hope I don't put bias into the study, but I certainly want this to be medically sound. We're going to be doing clinical trials with Emory on this in probably the next 12 months. We will be publishing a

number of articles in scientific medical journals over the next couple of years on this. It takes a whole lot of time and effort to analyze this data, as you all know. It has to be done in the best way possible. We're trying to bring good heads, good people in to help us do that.

Dr. Dattner: Is all this treatment under clinical trials, or do you have any open protocols available?

Dr. McCoy: We have total open protocols on this today. We can stay within FDA guidelines, so therefore we can offer this to any patient on an open protocol study today. The nice thing about that is that these patients can take anything else. What we're after today is saving a patient's life. Until we get into clinical trials, where we have to say you can only take our treatment, we have patients who are taking lots of things. We don't know whether the numbers we're showing are just our treatment alone or combinations of others, but we don't care today. We want to help the patients. We have enormous data collections on every patient. We know everything they're taking.

I know if it was my child or my wife, I really wouldn't care what saved his or her life. I'd want it saved. I come from the very conservative traditional school of medicine, the National Cancer Institute. But a number of us are faced every day with the devastation this disease causes and the complete devastation of the entire family. It's hard for a human being to say, "Let's just do it this way. If my way doesn't work, or if chemotherapy doesn't work, just get lost." Minds are being opened today that we've got to look at people as human beings.

Dr. Dattner: This is very much why we have such a big interest in this meeting. People have been very fed up with what turned out to be limited protocols for cancer that were available, either clinically in the office at the University Medical Center or what not. We find more and more people who are going out on their own, researching on the net and coming back and adding to their own protocols. That is truly what's being done, even in the University Center.

Although people think they're doing closed protocols, they're really open protocols, too. Those people aren't going to let anything past them. That's a real challenge. What a lot of people think from their perspective to be all that's going on may only be partial. They may be missing, because of that limited perspective, a lot of what really is happening in the additive success. Certainly things I've seen from the AIDS community show that the people who are living long do everything. They don't let anything stop. They get out there. They'll do the strong stuff. They'll do whatever they feel might help. Let me move on quickly, because I want to ask Josef some questions.

Dr. Beuth: I don't totally agree with this. Open studies are very good to get a trend for a treatment modality, but if you want to stabilize this trend you need a defined study. You need a certain group of patients. You need a certain tumor entity to make your study and to see a result. You must make it prospectively. What we heard can just be a trend and can just be the reason for further study following good clinical practice.

Dr. McCoy: I don't want to leave the impression that I do not adhere to that theory, too. That's the reason we have plans on the books to do clinical trials. As Ralf was saying in terms

of the Coley's toxin, if our arms were tied today just to do a clinical trial on Coley's toxin, it would be dead. And that may be one of the most significant breakthroughs in getting our heads cooking towards immunology that was ever done. I agree with you fully. Yet we have to look at what can we do today and what can we learn today from the past.

Dr. Dattner: I think we're also here because we accept both aspects. When it comes to making that life and death decision, we do look at data. We look very hard at data and say, "Yes, this data looks like this particular trail works. I may or may not add something in, but I want to start with that." All of us are participating in both worlds when we're making these decisions, so I must move back to the position that we do need both. The open aspect of the study generates a new question, or a new perspective, in terms of choosing indicating factors for which pieces one assembles in putting together a total picture.

The most exciting question is how one chooses among a palette of effective techniques those things which are going to work best for a specific instance. For things that came up like Ralf's statement about certain individuals whose histories are absent of febrile responses, there's one very simple historical question which can be asked in a work-up of a patient. This isn't rocket science. This can be an indicator that certain types of therapy, for instance the induction of fever by either adding it from a heat source or by adding it from a Coley toxin type of response, might be more useful.

As we begin to get simplified methods, a simple historical piece of data can indicate which direction, not just the specific antigenic questions. As we assemble sophisticated laboratory as well as simple historical questions, we're going to be able to put together a better palette, a better protocol for creating combination treatments.

Let me ask Dr. Beuth some more questions. There was a question about using viscotoxins. There were also questions about combining his treatment with the mistletoe extract with autologous tumor associated antigen in any animal models.

Dr. Beuth: We have no experience on the viscotoxins yet. It's another substance which is cytotoxic, but it's less cytotoxic than the mistletoe lectin 1. That means the cytotoxic activity is not so great. A problem is that the viscotoxins cannot be standardized so easily as can be done with the mistletoe lectin 1. That's why we didn't focus on this substance yet.

We have not yet combined the mistletoe treatment with the tumor vaccination. Within our society in Germany we have a big range of these tumor vaccinations. We have big studies done and we have positive results for renal carcinoma in Germany at the moment. We get the application or the allowance to do this tumor vaccination in all patients with renal carcinoma at the moment. We are doing quite a lot in this area.

That's why I contradicted a bit to these open studies. Our most prominent German cancer center in Heidelberg was involved in these studies. They made open studies in the beginning and had fantastic results. But afterwards when it came to controlled studies they had no more positive result. That means there are certain subjective elements in these open studies. You need a controlled study to confirm these data afterwards.

We didn't combine the two immunomodulating possibilities. In Germany, if we do combine the tumor vaccination with a low dose of chemotherapy to suppress the activity of suppressor immune cells, we combine it for instance with BCG, with another immunomodulator which is very potent and which can aggravate the activity of the tumor vaccination. We combine

it with the Newcastle disease virus, which was the topic of the first talk today. But we didn't combine it until now with the mistletoe lectin.

Dr. Dattner: You said in your open studies you had better results. Was that because it was a poorly controlled study, or because it's possible that there were some other additional factors that might have been individual-specific that worked better?

Dr. Beuth: I cannot exactly tell you, but those people who get a tumor vaccination in Germany are very special people. They care about their disease. They get information before they get operated. You must take the tumor, go to a center, ask your surgeon to conserve the tumor and send this tumor to a special center. You must do it all alone as a patient in Germany. These are very special people. This may be like a placebo effect, or psychological effect, or some other effect which is not due to the tumor vaccination.

Dr. Dattner: Or there's a bias for the people who most want to live, and the people who are most resourceful. This is what we've seen, and these are kinds of things that have to be factored in. Certainly everybody has met patients in this type of work who really have their tumor as an excuse to check out. Their life has come to a point where they don't want to continue. That has to be factored in ultimately. When somebody doesn't want to continue, even though the family may try to put them through the charade of trying everything, those people are going to respond differently. We've heard information earlier today at the plenary sessions suggesting that.

Dr. Beuth: A problem with these open studies is that you have a lot of different tumor entities, a lot of different tumor stages. It's very difficult to compare it and to make a result out of this. If you take these patients, you need a pair matching with other patients of the same tumor stratification. Maybe then you can make a decision whether it works or not.

Dr. McCoy: You're going back to what I was taught, which was pure scientific method. I agree with you. We have to ask ourselves what our goal is, what our specific personal goal is. I did those studies. I was involved in a lot of clinical trials, immunotherapy. We published lots of articles. Basically I agree with all that. It got to the point where I was tired of just doing clinical trials and seeing patients die. That's the reason my goal became, "Can I save patients' lives?" Whether it's a placebo effect or whether it's because these patients have a greater desire to live is okay with me. It feels good when I know that I'm helping save a patient's life. It will ultimately boil down to clinical trials as to how effective this treatment is, but I can guarantee it's going to have a specific effect also.

Dr. Dattner: Let me ask few questions for Dr. Kleef. There's a question about how your fever therapy was administered, especially the local. Also, was there a difference in how it worked if you used Coley's toxin versus another kind of a source?

Dr. Kleef: The route, timing and dosage of administration of Coley's toxin varied over the decades. We know a lot about it, and there is a rationale for every approach. Coley injected the Coley toxins into the tumor; he injected it subcutaneously; and later in his career he went on to the systemic treatment, which means he injected the toxins into the bloodstream. There's a

rationale for giving it subcutaneously because the toxins are being released slower into the circulation, whereas when you give it systemically you raise a fever response in an hour or so.

Also the timing of administration played a crucial role. There is actually no consensus on what is the ideal. Coley favored aggressive continuous treatment over months. Ideally the patient would be in a fever state for months. No patient can take this. In our clinical work in Germany – and we haven't had the funding to do trials – we offered Coley toxin treatment not more than once per week. The preparation we used, vaccineurin, which was actually streptococcus pyogenes and serratia marcescens, wasn't what we consider to be the ideal toxin. Josef Beuth is a world expert on Propionibacteria, another preparation. Yet we know that Coley's ingenious idea was to combine a grampositive and gramnegative organism. We would need much more funding to study the ideal route, timing and dosage of administration. The knowledge of how to put these trials together is there.

Dr. Dattner: Was there any evidence that certain people responded better to certain bacteria than others? Did there appear to be any type of specificity?

Dr. Kleef: We haven't studied this systematically. What I know from the literature and from personal experience with a couple of hundred cancer patients is that there was a missing history of fever. It can be very difficult to induce a substantial fever in the initial phases. We often needed to titrate the toxin to a dosage where those patients would respond. It cannot be said that a patient who gets a fever very quickly has a more favorable prognosis as opposed to a patient where we would need a series of three or four weeks to induce a significant fever response. Yet there are significant differences, and we don't know where those differences come

from. If we knew, we would be much closer to understanding why fever and cancer are inversely correlated.

Dr. Dattner: There was a disproportionate success with sarcomas. Do you have a reason for that?

Dr. Kleef: One hypothesis is that it is the embryogenic or mesothelial origin of sarcoma patients. Again, we don't have any explanation of why that would be. We do know that cancers of embryogenic origin had the most favorable treatment in Coley's toxins, such as ovarian cancer, which is of the same origin. Probably those tumors are more immunogenic. This is always a big topic, which tumors are more immunogenic.

The reason we know most about renal cell cancer and melanoma being immunogenic tumors is that we studied them mostly because we don't have any aggressive chemotherapeutic regimens available which make sense in these tumors. This is why those tumors have been labeled immunogenic. What we know from the induction of heat shock proteins – I'm not making any advertisement because this is a scientific thing, but there is a heat shock protein conference in Connecticut coming up this October. This is one of the most fascinating fields of research nowadays, to understand how hyperthermia, endogenous or exogenous, can actually induce what we call chaperoning antigenic targets to the cell surface. Whoever is interested can ask me.

Dr. Dattner: Thank you very much. I'd like to again thank all of the presenters for their presentations, and all of you for your comments and for staying on here. Thank you again.