

Comprehensive Cancer Care: Integrating Complementary & Alternative Therapies
Issues in Research on Complementary and Alternative Cancer Treatments (Part I)

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Dr. Jonas: *(The beginning of Dr. Jonas' presentation was not recorded.)*

In the area of practice, you also need to have the practice well-described and characterized before it can be studied. Klaus Linde from the University of Munich did a recent meta-analysis looking at the effect of acupuncture on asthma. He found that out of fourteen randomized controlled trials, only two of the trials actually used the same points. They did not use them in the same sequence or the same dose. All of the other trials used completely different heterogeneous methods. So one could not make a statement about acupuncture. One could say these points under these conditions with these patients, given at this frequency or this dose, had this kind of effect. But there may be no other trial that demonstrates that same kind of intervention. The description of the practice itself is important.

The third point is that expert documentation of diagnosis, previous and concomitant therapies, and outcomes must be systematic and objective. I'll talk about this a little bit when I refer to one type of investigation called the best case series. In this, individuals bring in case reports to demonstrate and document that 1) the person had cancer; 2) they were treated with the therapy and not with something else; and 3) whatever outcome was being measured – whether it's that the cancer resolved, quality of life, etc. – was measured in a valid way. Frequently there are holes in that evidence. It is not easy to collect that kind of evidence.

This leads me to the fourth point. If you're practicing, if you're delivering a service, you have a different goal than if you are trying to collect information for research. Hardly ever is

information that you simply go in and get out of a practice of the same type that you need in order to be able to document those effects. They're done for different purposes. If you go in and try to get information out of charts, for example, very frequently the information that you need to verify that the treatment actually occurred is not there. In other words, even to get things out of practices, you have to set it up almost ahead of time to get that out of the practice, in order to make sure that what you're collecting and documenting actually occurs.

I'd like to hold up a book that probably many of you know. It's called *Remarkable Recovery*, by Caryle Hirshberg and Marc Barasch. This is based on a very extensive documentation effort by the Institute of Noetic Sciences. I see Marilyn Schlitz in the back who runs their research section. They tried to follow cases, or at least collect as much information as they could about what they considered remarkable or unusual cases of spontaneous recovery in severe diseases. Many of these were advanced cancer cases. It's very interesting reading and very well documented.

The final analysis is that almost everybody used multiple types of therapies, in different sequences, for different purposes, at different intensities, etc. Attributing a particular effect to any of the recoveries is practically impossible. This is really what the goal of research is. It's to get to the point where one can identify more clearly what is actually resulting in the effect. What is the contribution, what is the attribution of a particular intervention to an outcome? To do that, you have to begin to split up what is actually done to control for a variety of factors.

Let me give you an idea of the types of research that we're going to be talking about, the examples that will be presented in those types of research, and the issues that will come up in our discussion. In the middle boxes is a series of types of research, each of which produces different kinds of information. Generally these types of research have to be done in a certain order. If

you move over towards the right-hand side, you get more definitive information. It is also more costly, more difficult to get that information. You don't want to invest, and sometimes cannot invest, in the more definitive types of research on the right-hand side than on the left-hand side.

Let me describe a few of these. First there's a considerable amount of developmental work. I illustrated some of these briefly. You need to be able to describe what the practice or the product is. You need to know what its characterization is. You need to know what the diagnosis is. Your outcome measures need to be developed. In some cases a lot of the developmental work involves simply developing a relationship with the individual who can do the research and/or deliver the practice, getting together and dialoguing with them. I hope that tomorrow Mary Ann Richardson will talk about the kind of developmental work that the Texas Center for Cancer Research and Complementary Medicine has been trying to do, simply to enhance the opportunities to do research in these areas.

The second area is the best case series. The best case series is an evaluation for collecting preliminary evidence on possible efficacy or benefit from an intervention in cancer, when no particular data already exists to help support that. This is something that was developed at the NCI. They have run a number of these. We are in the process of working with them to beef up the system so that more individuals can use it. It involves collecting best cases of treatment and cancer response. This usually means objective tumor response or survival. It is often difficult to document other kinds of outcomes and know what they mean without a comparison group.

A practitioner who feels they have a usable therapy for treating cancer can collect documentation that at least ten cases have responded to their particular therapy. Usually not very many are required; ten is an average number. We provide guidelines to the practitioner as

to what needs to be collected. In some cases we work with the practitioner to help them understand what kind of documentation is needed in terms of diagnosis and making sure that we know all about what other types of therapies are used separately. When sufficient information is collected, then an independent panel is assembled to evaluate that. The panel does an independent analysis of that information to see if, in fact, it does represent some effects, or it is possible that it likely represents some effects. This is the best case series.

Dr. Cassileth is going to talk about case control studies, and some others in which one selects cases, usually in a prospective manner. If you have the documentation, you can do it in a retrospective manner. You select controls (individuals with similar diagnosis who did not receive that type of therapy), and compare what the outcomes were. There are phase I clinical trials, which I didn't put up here. These generally are trying to make sure that the product is not largely toxic and to get some idea of what kind of dose would be used. Frequently we don't have this information. If you talk to private practitioners who use a particular product, you often get a very wide range of recommended doses as to what's effective and what is not. Phase I trials are an attempt to get more definitive information about that.

Phase II trials are essentially screening for effects on cases. Usually a single diagnosis is followed prospectively. You're looking at some objective marker, usually tumor reduction or survival. Usually there is not a comparison group, although there can be. These trials are not designed to prove a therapy. They're designed to indicate what therapies might be useful to put in more definitive research, called a phase III trial. That is your standard randomized controlled trial.

Let me clarify something here. You can do randomized controlled trials on just about anything. They don't necessarily have to be blind. Blinding is a separate issue. You can

randomize patients to things that you can't blind them to and still get a good comparison. They don't necessarily have to be on a single diagnosis, although that helps you control the concomitant other factors that might be influencing this. They don't necessarily have to be on therapies that are even similar.

There have been multiple comparative randomized trials comparing surgery to medical therapy, compared to lifestyle support, in cardiovascular disease, for example, looking for mortality and heart attacks. A randomized controlled trial is simply an attempt to get two groups that at the start are comparable, administer one set of therapies, either simple or complex, to one of them, and a different set of therapies, simple or complex, to another, so that one can actually do a comparison.

Finally, a meta-analysis is usually a statistical technique for trying to see how much confidence we have in the results of the trials that are done. In many areas of clinical research there's quite a wide variation of effects, even in randomized controlled trials. For example, when the H2 blocker cimetidine first came out for the treatment of duodenal ulcers, the drug company sponsoring or promoting this did multiple randomized controlled trials, placebo compared, all over the world.

It found that in the control groups the placebo rate varied from 10% effectiveness all the way up to 90% effectiveness. The effectiveness of the cimetidine stayed at about 75%. This meant the studies in which the control group was 75% and above were all statistically negative. They were negative trials. The ones that had a low placebo response rate were all statistically positive. This left them in a very awkward situation of saying that in certain countries, like Germany, they could never prove it worked. In other countries, like Belgium, it clearly worked. This has to do with other kinds of factors which are difficult to control in clinical research.

Clinical research is being done on humans who have a variety of different factors that you cannot control. You do your best to control the ones you think are important. You hope the randomization process will control for the others. But it's still kind of a messy business. A meta-analysis attempts to take all of those studies and say, "How confident are we that a summary effect across all of those studies is true?" How reproducible is it, if you go from one trial to another, if a different practitioner is doing the therapy, if a different center is doing the therapy? What is the likelihood that they're going to get a similar type of effect?

This then is a series of types of studies. We're going to have examples from our panel members of almost all of these different types of studies, specifically with complementary and alternative medicine, and have a discussion of that.

Before I turn it over to the first speaker, let me highlight some of the issues that need to be addressed to do any of these studies. I've already mentioned a few of them. Collaboration is very important. You have to have experts who know how to deliver the therapy and have experience in it. You have to have those who know how to put together the study, do the statistical analysis, etc. We're talking about team research. Minimum documentation I talked about. Sufficient outcome measures I talked about.

Let me say a word about comparison groups. You always have a comparison group. If someone says they haven't got a comparison group it just means it's implicit rather than explicit. Whenever we look at even a case we're comparing it to something. It might be an expectation that it should have behaved differently. Or it might be a series of historical controls from our knowledge of a particular condition and what we expect. There's no such thing as a claim or a benefit without some kind of implicit or explicit comparison.

As we move along in the hierarchy of research, we attempt to make those comparisons more explicit and more detailed so that we can get more refined and specific information about what's going on. Otherwise it's underground; it's in our unconscious. Then there can be large room for debate based on the same amount of data. Comparison groups are there. The question is, how well did we control for them or what actually are they?

Reproducibility. Sufficient numbers I've talked about. You have to have sufficient numbers in clinical research, because such a wide variation of responses occur. Some of the basic science issues I've also mentioned. The product's characterization, stability, consistency, safety, mechanisms – that information is frequently essential before one can actually do a controlled trial and know that in the use of that particular product, for example, next time you've still got the same product.

I mentioned the example of garlic. We're currently doing a trial with the NIMH on hypericum – St. John's wort – and depression. We've spent a lot of time trying to make sure we have a product that is high quality, not contaminated, reproducible. We need to have a product with a reasonable shelf life and to know what that shelf life is and what actually gets absorbed, depending on how you package it, etc. That product will not necessarily be the same as the kinds of products you buy off the shelf right now, because they may have not been prescribed.

Finally, there are practice issues that have to be addressed before you apply this particular therapy to anybody else. Do you have information about the practice itself? Is it sufficiently described? Are there decision points for when to do it and when not to do it? Do we have information about other therapies that were occurring at the same time, or about compliance? Many complementary therapies, especially based on lifestyle and diet, are very

complex. They consume your entire waking time, and sometimes your sleeping time too, depending on the clock on which you have to take your pills.

Compliance is very rarely assessed. When it has been assessed, often it is much lower than what people think, even in conventional therapy. Even in simple drug therapies they have found that compliance frequently is only about half what's written on the bottle. Take it three times a day for ten weeks. This is true even for simple things like antibiotics for bronchitis or pneumonia or something like that. People usually comply fully only about half the time. The more complex the therapy is, the more likely it is that you're going to get less and less compliance. You have to assess that if you're going to say this has something to do with the therapy or not. Various kinds of other treatments are involved in that.

The first presenter has been doing research in complementary and alternative medicine specifically in cancer for a long time and has extensive experience in these areas. She used to sit on the Advisory Council for the Office of Alternative Medicine and made tremendous contributions to that. She's currently at the University of Pennsylvania. She's a medical sociologist. She has also served on a number of other organizations. She has been consultant for the Family Practice and Community Medicine Department at Duke University. She has been on the Advisory Panel on Unconventional Practices of the American Cancer Society. She has recently completed a book summarizing information about alternative medicine called *Alternative Medicine Handbook*, and has written numerous studies published in the peer-reviewed literature on cancer and complementary therapies. It is my pleasure to introduce Barrie Cassileth.

Dr. Cassileth: Thank you, Wayne. It is a pleasure to be here.

I'm going to try to illustrate, through the use of information about case control studies, and one in particular, many of the points that Wayne made. I hope that I'll be able to do this with my slides. The gold standard is a prospective randomized clinical trial. That's considered the ideal study involving human beings. In this kind of study you have a pretest and a posttest, in both instances using two groups, an experimental group and a control group. After the pretest you have an intervention, or you measure a characteristic, or you wait for a period of time, or you study a regimen, whatever the situation might be. Following that intervention or measurement you do a posttest of the people in the experimental group and those in the control group.

Ideally the experimental and control subjects are drawn randomly from a single pool after informed consent is obtained. You do this in order to reduce bias in your samples. Then people are randomly assigned to the experimental group or the control group in large enough numbers that you can have some faith in your data at the end.

This ideal research design has some problems. I did not make this slide for this particular talk, but I think that it's still quite relevant. Patients' clinical status sometimes limits our abilities to do a prospective randomized trial. Sometimes it's unethical or impossible to randomize patients. We have these difficulties in palliative care in hospice programs. Sometimes it's very difficult to locate a control group that really is appropriate given the kinds of things that you want to test.

Fortunately, there are other acceptable designs that will give us information in which we can have some faith. One is a matched control design. In that kind of study, for each subject a control subject is found. That subject is supposed to be similar in as many relevant ways as possible, except for the regimen, the method, the characteristic, for whatever you're going to

study. Sometimes subjects are used as their own controls. In that circumstance you have a patient who is given an intervention and followed over time, and then the pretest and posttest in that one patient is compared.

I'm going to tell you the story of the conduct of a particular case control trial. I'll take you through the methodology and the detailed rigorous way that one must go about developing and mounting and concluding a study. This particular study we are using because it involves an alternative method. It was called Survival and Quality of Life among Patients Receiving Unproven as Compared with Conventional Cancer Therapy. You have to state a very explicit goal when designing research. The goal here was to compare survival and to compare quality of life among patients who had end stage malignant diseases on alternative regimens versus mainstream cancer therapy.

We developed two hypotheses. If you turn the wording around they become research questions, which are fundamental. I try to make this point every time I talk about research. If you don't start out with hypotheses or research questions, everything else is going to be a little shaky. If you start out with clear, a limited number of research questions, your study will all fall into place.

Our first hypothesis was that there would be no difference in survival time. This hypothesis was based on the fact that these patients had widespread metastatic disease. We didn't think it was rational to assume, although we were testing it, that any treatment, alternative or mainstream, was going to prolong survival in these patients.

The second hypothesis was that quality of life would be better among the alternative therapy patients than mainstream treated patients. We assumed this because we thought many mainstream patients would get chemotherapy, which certainly decreases quality of life, would

get other treatments that might not feel very good and might create some problems. We thought the alternative therapy gives you more hope and would be less problematic with regard to physical difficulties and so on. Those were our two hypotheses. If you turn the hypotheses around, the questions are: Are there differences in survival time? Are there differences in quality of life between these two groups of patients?

Once you decide on a research goal and develop your research questions, you then have to select a particular methodology. In randomized clinical trials for cancer, the best available treatment is compared with an investigative treatment that has already been studied, as Wayne described, in phase I and II trials. It has already been studied for safety and efficacy. We know that it's not terribly toxic. We know that patients can take it well. We also know that it has some efficacy. What we don't know is whether it's better than the best currently available therapy. The goal is to compare and determine which is more effective.

In this particular study that we tried to do, we could not randomize patients to receive an unstudied alternative. It's not ethical. It would never get through an IRB, an institutional review board. It's simply not feasible. Therefore we had to find something other than a randomized clinical trial. We selected the case control study. The cases were patients who were receiving an alternative cancer therapy. The controls were patients under the care of oncologists at a major comprehensive cancer center in this country. It was a prospective study. The method was simply that we followed patients over time and compared outcomes in the two groups.

The alternative therapy that we looked at was the Livingston Wheeler regimen in San Diego. We selected that one for a variety of reasons. In large part it was because Dr. Virginia Livingston Wheeler, who is now deceased, was a marvelous woman and very eager to collaborate with us. She was very open to being evaluated, which you cannot say about many of

the alternative therapies offered for cancer. She also had a sufficient number of patients. That was very important. There were a variety of other reasons. We had good access to data. They were very open and willing to participate in any way that was necessary.

This regimen consisted of a vegetarian diet, 75% of it raw, no animal products whatsoever, coffee enemas, and some other odds and ends of things. The most important part of the regimen was an immune-enhancing vaccine which was given twice a week. This was the crucial part of the therapy. All the patients at the Livingston Wheeler Clinic who participated in our study had received standard treatment. They were end stage metastatic disease patients.

One must establish eligibility criteria for any study, regardless of the particular methodology. Our eligibility criteria for patients who could be accrued to this investigation included a number of things. First of all, we needed tissue biopsy documentation of cancer. We have some alternative diagnostic techniques which do not really diagnose anything. Many patients claim that they have been cured after they've received a particular treatment. People rarely ask, "How was your cancer diagnosed?" If you find out it was diagnosed by iridology or some other unproven method, that's problematic, so you have to have tissue biopsy documentation. This is true for any clinical trial that would be run in any mainstream setting with the NCI or a major institution or anywhere else.

Secondly, patients had to have a median estimated survival of less than a year. We wanted to be able to conclude the study in a reasonable period of time, so we looked for patients who had metastatic disease who were over age 20. They had to be aware of their diagnosis, and they had to be literate, with no brain metastases. They had to be willing to sign informed consent. If they were not, obviously they were not put on the study. They had to have pursued the alternative therapy for a minimum of one month, exactly as it was prescribed by the

Livingston Wheeler Clinic. Patients who did not use the therapy for a minimum of a month were dropped from the study. We ended up with a group of patients who met all of those criteria.

Then we ran into the big problem – the matching. This is probably the most difficult aspect of a case control study. You have to match on factors that are known to influence whatever you're looking at. In this case survival was the most important one, so we had to match on factors that are known in metastatic cancer to influence survival. Those factors are gender, race, age (we did an arbitrary breakdown, a median breakdown later of under 60 and 60 and above), diagnosis and the time since the disease became metastatic or recurred.

In the process of attempting to match patients we found 20 Livingston Wheeler patients who we could not match with patients from the University of Pennsylvania Cancer Center. We found 65 University of Pennsylvania patients who we could not match with Livingston Wheeler Clinic patients. Unfortunately, these 85 patients could not be included in the study, and they were not. All the unmatched patients were excluded. This really is a challenge. This is the agony of doing this kind of research.

You need a sufficient number of patients. You don't guess at this. I needed a statistician to look at it and tell me what the minimum number would be. There are certain statistical criteria that one must apply. You have to have a sufficient number of patients in order to properly answer your research questions. In our case, because of the difficulty of matching according to all the criteria that I just mentioned, the enrollment took us three-and-a-half years. That's a long time just to accrue patients to a study.

By the way, it took us a couple of years in the very beginning just to work out a relationship with this clinic and to determine how we could work well together. This was after I had tried to involve myself with other clinics that did not work out. It is a lengthy, arduous job.

We ended up after three-and-a-half years of accruing, with 156 patients, half each from the University of Pennsylvania Comprehensive Cancer Center and the Livingston Wheeler Clinic.

Our outcome measures were length of survival and scores on the quality of life scale called the FLIC, which stands for Functional Living Index-Cancer. This is a standard quality of life scale that was developed for use in cancer patients, and specifically for repeated use. This is very important. If you use a scale that is not developed for repeated use, patients will memorize the scale if you give it to them repeatedly. You'll get the same answers. This test was a particularly good one. Every two months until the patient died, patients were contacted by research assistants by telephone. They asked what treatments they were on, how they were doing, what side effects they were having, all the details of their clinical status. Also they were mailed the quality of life form to complete by mail.

The results are the least important part of this presentation, but I want you to have the information. We found, as expected, that survival did not differ between the two groups. The yellow curve represents patients from the Comprehensive Cancer Center. The red curve represents the alternative therapy patients. You can see that the curves overlap. There were absolutely no significant differences, but this is exactly what one would expect.

There are two ways of looking at this. One is to say that the alternative didn't do any better than mainstream treatment, which is true. But the other way to look at it is to say that mainstream treatment didn't do any better than the alternative therapy. It's a cup half-empty, half-full situation.

The second hypothesis regarded quality of life. Here we had a big surprise. We found that quality of life scores were higher, as you can see in the yellow bar, among the cancer center patients than among the Livingston Wheeler patients. This was contrary to our hypothesis. We

conducted every statistical test known to mankind that was appropriate to try to get a different result, but we could not. We determined, when we looked very closely at the data, that patients from the Livingston Wheeler clinic were getting sick from their regimen, just as patients might get sick from chemotherapy.

We also believe that there was a great distance between expectation and reality, and that a terrible disappointment occurred when reality failed to live up to expectations. That is, patients went there assuming, or at least hoping, that they would be able to extend their remissions or achieve a cure, even though the Livingston Wheeler Clinic was clear that they did not have the magic bullet for cancer. The reality was that didn't happen. That discrepancy was very troubling and problematic for patients. It influenced their emotional status and therefore contributed to lower quality of life.

Despite the care with which we attempted to conduct this study, there were some biases. These biases are frequently associated with many studies, case control and other kinds. One was the fact that random assignment was not possible. Patients were self-selected in the use of the mainstream or alternative treatment. Patients decided to go to one or the other. This is a self-selection bias.

A second kind of bias is called interviewer bias. I'd like to illustrate that in a minute. The point is that the telephone interviewers were not blinded to whether the patient was a Livingston Wheeler patient or a Cancer Center patient. That was impossible because of the information that patients gave over the telephone and that interviewers had about the individual and the location in the United States. These were patients from all over the country.

Also, as is true in most investigations, certainly this one, results cannot be generalized beyond patients who have extensive metastatic disease. That is, we don't know whether we

would get the same results if we treated patients who are early in their disease, or mid-way through their disease. Also, the results cannot be generalized to other alternative therapies, only to the Livingston Wheeler treatment. So there are biases.

Now I'd like to give you an example of a case control study that I attempted to do and failed in completing. This was very sad for me, because I wanted very much to study this therapy properly. This was IAT, which stands for Immunoaugmentative Therapy. This treatment was given in the Bahamas years ago, and was very popular at that time, by Dr. Lawrence Burton.

Unfortunately, the therapy was secret. That always raises a red flag. We don't know exactly what it consisted of, although we know in general what it consisted of. But that's really not relevant to my point. We had a tremendous problem in that we could not randomly accrue patients who had been treated at that clinic, because we only had the names of patients who were alive. Those patients could be contacted, but obviously the patients who were deceased could not be contacted. This was a major problem in sampling bias.

Secondly, when we talked to the subjects we found they were not clinically similar. They varied particularly in time since they developed metastatic disease. We know that that's a major survival factor, so that would greatly bias any results. Finally, there were only 29 patients for whom we had complete records documenting their metastatic or inoperable disease at diagnosis. That is, only 29 patients met the eligibility criteria for this study. That's just not enough to develop a real study.

This is one of my failures. I point it out as an example of the difficulties of doing things properly, so that you can have faith in the results. I guess we could have reported on the 29

patients, or even the whole group of patients. But the information would not have been sufficiently valid to be worthwhile. That's unfortunate, but that's the way it was.

Let me tell you about a couple of guidelines for conducting research – no's and yes's. In developing the research question, which is the single most important job that we have, we have to be very careful and very clear about what we want to study. The no aspect of this is when people get together and say, "Let's study patients' emotional status and document how they're doing psychologically." That's not the best approach.

On the other hand, a better and related research question would be: Does the patient's emotional status change as a function of extra volunteer visits, for example, as an intervention? The hypothesis at that point would be that patients receiving x number versus one volunteer visit per week would show better emotional status. That's just an example, but it shows how easy it is to develop a research question that's really not going to be testable. Everything will fall in place if you ask a clean, well-defined research question.

Another problem, another issue to consider is that you want to determine the sample size that's needed to answer the question. This is very important. You don't say, as many people have a tendency to do, "We should be able to get 10 or 15 patients in each group, and that sounds like it's enough. Let's go with 10 to 15 per group." That won't do it.

Instead, we have to statistically determine a clinically meaningful difference between scores on whatever we're doing, a questionnaire or whatever. We need to know, from that information and from statistical analyses, how many patients are required to show the amount of difference that's clinically meaningful. I have to check with a statistician, because that is certainly not one of my strong points.

We want to avoid interviewer bias. We want to avoid having one interviewer come in and say, "Hi. You're looking really good today. Let's get started with our study," or having another interviewer go in to the next patient and say, "I understand that things haven't been going very well. I'm really sorry to bother you, but could we go through this questionnaire?" That is real interviewer bias. If you heard Herb Benson's talk yesterday, you know what kind of expectation is set up in the minds of patients by the way health care professionals talk with them. Instead, you have to have identical questions asked, hopefully by the same person. If it's in writing, you ask in the exact same words. Then you do not have any variation in expectation or understanding from patient to patient. In that way you avoid interviewer bias.

Maintaining careful records is important. I know many of you in this room have conducted research and you know about this. But I run across an awful lot of situations where there are not records. They have to be maintained with extreme care. In data analysis, we don't want to go according to the no side, which is to always use t tests, or chi square, or whatever to analyze data. Instead we want to look at the kind of analytic techniques that are most appropriate for our kind of data. Again, I think a statistician is required.

That's the end of my presentation. I hope I've given you a sense of the agony and the ecstasy of going through this kind of investigation. Thank you.

Dr. Jonas: Thank you, Dr. Cassileth. We will have ample time at the end for discussion, so please save any questions you might have, except for me. I'll take a prerogative right now and ask you one question. In your power analysis, first of all in the quality of life, were you powering it off the quality of life outcome or the survival outcome?

Dr. Cassileth: Quality of life.

Dr. Jonas: Were the differences in quality of life statistically significant or not?

Dr. Cassileth: Yes, very.

Dr. Jonas: It sounds like when the group entered in they already had, or at least were reporting, differences in quality of life. Yes. Right.

Our next speaker is Dr. William Regelson. I didn't know Dr. Regelson before this afternoon. I just met him. I did a literature search and was flabbergasted to find the extensive publications that he has in a variety of areas. They include some very early research in the area of complementary and alternative medicine for cancer, which he continues. Dr. Regelson is Professor of Medicine at the Medical College of Virginia in Richmond. He's a specialist in medical oncology, and he has joint appointments in microbiology and biomedical engineering. He has been a leading researcher in the field of aging for over 20 years. He's formerly the scientific director of the Fund for Integrative Biomedical Research, dedicated to research on the biology of aging. He's going to talk about some of the research that he has done in some of these areas.

Dr. Regelson: Thank you, Dr. Jonas. First of all, I want to say that if we really have a good anticancer agent, we'll have the experience that I had in 1965 when Don Pinkel was recruited to organize St. Jude's Hospital, the Danny Thomas Hospital in Tennessee. Pediatric oncology at Roswell Park Memorial Institute did not have a pediatrician to run the program.

Back in 1965, to find a pediatric oncologist was very difficult, because all the children died. Very few pediatricians enjoyed the practice of treating leukemic children primarily or lymphoma-burdened children. So I got the job of running pediatric oncology.

I'm an internist. I was very fortunate, because I was among the first in the United States to have available vincristine, the alkaloid from the periwinkle vine, to treat acute lymphoblastic leukemia in children. I had seven children on the unit, all dying of acute lymphoblastic leukemia. Every one of them went into complete remission, coming back from the dead. It was the most glorious moment of my life. I didn't need 18 patients, 20 patients, or 100 patients to see a result.

I've always been the optimist relative to what I'm looking for, what I want to see. For example, I sat on the panel this morning in regard to trophoblastic markers, where Hernan Acevedo presented his work in regard to chorionic gonadotropin beta. If he's correct, we have a final common pathway defining malignancy as related to pregnancy. We have now the development of monoclonal, cytolytic, cytotoxic antibodies, which may make a tremendous difference, not only diagnostically but therapeutically. Of course that's what I'm looking for.

Among the things that alternative cancer people should look at, and one of the things that I would like to see the institute involved with, are some of the problems related to the egocentric attitudes of some of my colleagues in medical oncology. For example, David Blask reported yesterday. He does very elegant work in Cooperstown in relation to the role of melatonin as an anti breast cancer agent affecting estrogenic receptors and response of estrogen dependent tumors.

Lissoni in Milan has been treating cancer patients with melatonin for quite a few years, combining it with immunotherapy. He has been reporting excellent results, although the

numbers are small. But nobody from the U.S. goes there to look at Lissoni's work, and there is no major interest and enthusiasm for melatonin. Melatonin has been clouded by getting it over-the-counter. I played a role in that. I didn't expect that to happen, but my interest in melatonin as an anti-aging hormone led to that. It's all over-the-counter for sleep induction and for antioxidant and other properties. So people are not that interested in it.

What I would like to see happen is this: if somebody's reporting somewhere in the world a result that looks promising, we should be in a position to travel somewhere and to look at other people's work on-site, on the scene. (Our colleague just reported on Burton, who I thought was a crazy man. I actually went down to look at Burton's efforts and was very disappointed with it.) We need to render judgments that are not necessarily related to it not being invented here, not being a U.S. product, representing somebody else or some peripheral fringe individual.

There is another thing which is always a danger related to what we're doing, because we're trying to meet FDA standards. When dealing with natural products, with herbal products, you've got to remember that although you need a standardized product, the absolute purity has to be a relevant thing. Here's one of the big problems that we're faced with. I've done a lot of work in the antiinflammatory field, with compounds that affect phospholipase A2. These are antiinflammatories which also have antitumor activity.

We have natural products which are isomeric. They're mixtures. The mixtures are better than the pure synthesized product. Because of FDA standards, we had to get a polymer chemist and spend a fortune to make a synthetic product, when the natural product would be better. We have to keep in mind that the body works through diverse molecular interactions. Sometimes mixtures are better than single pure agents. For example, I go back to the days when we used to use digitalis whole leaf. You could tell when you got too much on board because patients

vomited. Now we're using the purified alkaloids, digitalis preps that are synthetically made. You have to use blood values to determine where your patient is headed. Keep that in mind.

Very quickly I want to open up an area which speaks to a failure in my life, 40 years of work that essentially went down the tubes. But it's going to turn around. The point I'm trying to make is that the route of drug administration is critical. When you're dealing with natural products, if you're dealing with alternative medicine, you're going to want to shoot for an oral route, because if you go IV you're going to have to deal with essentially a purified material that meets FDA criteria. Yet oral absorption may not be quite what you want.

I now want to talk to you about something that has developed which is the intraperitoneal route. I think one reason we failed in the area of cancer chemotherapy and immunotherapy is that we've neglected the abdomen and peritoneal introduction of drugs as an access to therapy, as a vehicle for treatment. With peritoneal dialysis there's going to be a major change in what's going on in the clinic relevant to treatment. I'm going to go very fast, because I just want to summarize. This deals with theory in regard to jelly coat substances, which ties in with chorionic gonadotropin as a charged molecular surface.

Let's go to the first slide. These are transplanted mouse tumors, a single syngeneic tumor. Chemotherapy was given on the right intraperitoneally. It's contrasted with the controls on the left. You can see there was some level of inhibition that did not relate to weight loss.

The next slide shows the standard tumors that we used to use. These are transplanted syngeneic tumors that were the standard anticancer screens that we used to use back before the mid-80's. Then suddenly somebody got the great idea that the tissue culture technique was the way to screen. I think that is a bunch of nonsense, but it's still an ongoing thought. This was what we used to use.

We injected chemotherapy or immunotherapy (initially I was involved with chemotherapy) into the peritoneum of the mouse. It's easy to stick a mouse in the abdomen. You didn't really run that great a risk of perforating the gut, versus sticking it into a tail vein. Next slide. Here again, cell production versus cell loss, tumor size. That's standard. Let's go to the next slide.

We have to recognize that the tumor burden is a key factor governing our response to therapy. This shows you what happens if you have residual nodal disease in breast cancer relevant to the character of survival. The mass of residual tumor plays a major role governing the pattern of survival to whatever therapy that you involve yourself with. Next slide.

Exposure time, how long the drug is in contact with the surface of the cell, is a very critical factor in regard to chemotherapy. That's one reason I'm skeptical about *in vitro* screening. The time elements are arbitrary and not related to the pharmacokinetics of what's happening to the individual patient when a drug is being secreted and moved about by circulation and kidney response. Next slide.

This is heparin. Heparin is coming back in another form in terms of low molecular weight. Heparin, from the point of view of anticoagulant usefulness – I became interested in heparin-like compounds because of their charged polyanionic electrically negative nature and their resemblance to the jelly coat substance that surrounds the unfertilized egg, the removal of which starts cell division going. Next slide.

This again relates to angiogenesis. There you see the growth of blood vessels and the tumor in the center. What we're looking for, again related to Folkman's work, is angiostatin and compounds which can block the growth of the vascularity that supports the tumor.

The next slide shows corticosteroids in conjunction with heparin that inhibit angiogenesis. Here we are at this stage of our clinical existence, waiting two years for the appearance on site of a new product, a peptide developed by Antremed, which got big publicity as being a cure-all. It's not Folkman's fault. It had a profound effect on their stock and setting up a level of expectation which was disappointed because we're dealing with mouse tumors. This is mouse tumor work. But heparin is available, and so are these steroids which interfere with angiogenesis. What are we waiting for? Next slide.

These are some of the synthetic polyanions, which are heparinoids that I looked at in a tumor screening. We're going back between 30 and 40 years. Next slide.

This is what we saw clinically, hemorrhagic necrosis of tumors. This happened to be reticulum cell sarcoma. Next slide. This is the compound we did the most work with, divinyl ether maleic anhydride copolymer, which was a Hercules polymer developed by this chemical company for other purposes in the plastic industry. This breaks up to form a negatively charged polycarboxylate. Next slide. It had a variety of effects against transplanted tumors but also activated macrophages which then killed tumor cells. It acted on host defense mechanisms. Next slide.

Everything I'm showing you here is intraperitoneal injection. We see a number of effects. This is polyoma virus, which is a DNA virus that causes a wide variety of tumors in sensitive mouse models. We could block that with the presence of this polymer given intraperitoneally. Next slide. We gave it clinically to close to 1,000 patients with several million dollars of National Cancer Institute, Monsanto and Hercules funding for these polymers that were looked at clinically. We induced the interferon. We got occasional tumor response, but we went from IP to IV.

Why did we do that? We did that because we were afraid of the intraperitoneal route. The peritoneal space was considered a sacred area. We were afraid of sticking a viscus and getting peritonitis. We were afraid of getting fibrosis and occlusions of the gut, as a result of putting drug in there. But that has changed now because of peritoneal dialysis, which is becoming standard therapy for the treatment of renal failure. Next slide.

This again is the fact that if you go IP you can block hepatic metastases. One has to start thinking of the adjuvant use of these polymers intraperitoneally, which gives you ready access to liver circulation and to the effect of small metastatic foci to the liver. Next slide.

The other thing these compounds do in the right environment is produce apoptosis. I discovered apoptosis, but I didn't know what I discovered. I called it the orgasmic death of the cell, reported in *Experimental Cell Research*. I could have been a contender. I missed it completely. Next slide.

This again shows dose timing and the therapeutic index for the IP injection of this material. Quite a good therapeutic index intraperitoneally in the mouse models that we looked at. Next slide. These compounds, these polyanions affect reverse transcriptase and a whole host of enzymes involved in DNA synthesis. They affect not only host resistance, cell surface interreaction, but also affect enzymes critically involved in tumor growth but also in viral proliferation. Next slide.

The key point I want to make is that everything we did in the mouse was IP. We went clinically; we did dog toxicology; and we went intravenously. We wound up with shock, what's called colloidoclastic shock. We wound up with leukopenia, thrombocytopenia, hemorrhage, renal failure, prostration, shaking chills, vasculitis. The therapeutic index of these compounds was a disaster.

Suddenly it dawned on me back in the mid-80's, just before peritoneal dialysis hit its popular phase, that maybe we failed clinically because we went IV. It's too toxic intravenously. Let's go IP. So we did a C14 tagged polymer. We found a completely different pattern of distribution IV versus IP. When you give it IP, it's held in the retroperitoneal nodes. It stimulates peritoneal exudate cells. It's carried by the diaphragmatic pump into the mediastinum up into the thymus. It covers 80% of the lymph nodes of the body. Next slide.

This is the future. This is a Portacath subcutaneous port placed into a patient with a Tenkhoff catheter that will go into the peritoneal space. This is where chemo and immunotherapy is going to take place. I want to show you some more of the virtues of the route of administration being critical. Next slide.

This is work from Richmond and Campbel on Plum Island where we studied the effect of a hoof and mouth disease vaccine in rats. It was a rat vaccine, although hoof and mouth disease is obviously a disease of cattle. The model system was a rat. The vaccine was essentially useless, but when we gave the vaccine intraperitoneally together with our polymer, we got an effective vaccine.

The next slide shows protection against Herpes Type II in a mouse model. When we gave a vaccine in association with intraperitoneal Pyran copolymer, this polyanion, we got protection. The problem is, for example in the hoof and mouth story, Hercules went intramuscular. They didn't want to stick cattle intraperitoneally any more than we want to do it clinically. So it never moved as a vaccine adjuvant approach to treatment.

The next slide again shows the value of these polymers given intraperitoneally. This is BCNU, which is a nitrosourea antitumor agent. When you combine it with this chemotherapy

using these polymers which stimulate immunity and have antitumor activity in their own right, you get a true synergy with remarkable inhibition of tumors. Again, IP, IP. Next slide.

This relates to activation of macrophages killing Lewis lung cancer. Again the IP route stimulates the peritoneal exudate cells which will kill your tumor. Next slide. This shows how these polymers combined with enzymes, in this case Pyran copolymer is put together with superoxide dismutase and given to mice with influenza. It protects against influenza by providing an antioxidant which is carried to the lung by the polymer. These things can be used as carriers. Next slide.

This is where I'm going to present to you what is current and is going to play a major role in changing our attitudes towards chemo and immunotherapy. This is from the ML corporation in London. I just got back from the UK. These people have an Icodextrin, a polymeric dextrin, which is made from malt. Icodextrin is used as a peritoneal dialysis solution which Baxter Laboratories is going to be developing in this country for peritoneal dialysis. It's an ideal vehicle for delivering chemo and immunotherapy to the peritoneal space through a Tenkhoff catheter by way of a Portacath. Next slide.

This is the most exciting thing. This is from the Hammersmith Hospital in London. Reduction of a viral role of HIV 1 after intraperitoneal administration of dextrin 2-sulphate in patients with AIDS. The next slide shows the remarkable decline in virus titer using dextrin 2-sulphate, a charged polyanionic dextrin, put in the Icodextrin. This is done three times a week. The peritoneal dialysis fluid is allowed to resorb without being removed. It's having an effect in producing a disappearance of positive virus titer and improvement clinically in some patients. It's early. It's too early to make any major claims for it, but it's in the right direction.

The next slide shows the concentration, which relates to where you put it, IV versus IP. If we had followed our program in the mice by going IP and then translating that to the human condition, we'd be in better shape.

I'm grateful to Dr. Jonas for giving me the opportunity to point out that we have to think hard about our experience. We've always been translating an intraperitoneal mouse study to an intravenous human study. The IP site has its own virtues. Now, thanks to this new technology of the Portacath Tenkhoff and peritoneal dialysis, we have a new approach to the treatment of cancer that we should be aware of. Thank you.

Dr. Jonas: Thank you very much. Dr. Regelson illustrated a number of items for discussion in both of these talks, especially the importance of looking at a variety of types of evidence, both basic science and clinical, and not assuming that a particular type of basic information will necessarily translate itself into clinical results. Certainly in cancer we're coming to realize this more and more. Simple tumor responses in cell culture or even in animals do not necessarily translate themselves into clinical results. On the other hand, that information may help guide us specifically in trying to maximize the effects that we would see in patients.

Before I open it up for questions and discussion, I'd like to ask any of our panel members if they have any comments they would like to make. In our next session we are going to have Dr. Mary Ann Richardson and Professor Beuth speak, both talking about some of the developmental issues that go into this and some of the randomized controlled trials. We'll be doing that tomorrow morning. I'd like to offer any comments or discussion or questions that the panel members might have before we open it up to the audience.

Dr. Richardson: I'd like to make one comment. We are doing a number of things at the University of Texas, at our alternative medicine center funded by the OAM, in collaboration with M.D. Anderson. Dr. Regelson, I wanted to let you know that we are planning to do a randomized controlled trial with melatonin, with lymphoma patients who are beginning a CHOP regimen. These patients typically have a very good clinical outcome. However, they are plagued with neutropenia and thrombocytopenia, lots of infections. We're using this therapy to see if it prevents those sorts of side effects of chemo. We have an IND. A protocol has been approved, and we hope to start in the next couple of months.

Dr. Regelson: That's very nice. The one concern that one would have is the antioxidant role of melatonin. If you're dealing with a pro-oxidant effect of your chemotherapy, that's something that you have to keep in mind. It might be an effect.

Dr. Richardson: What about the recent study where they combined it in the breast patients with chemotherapy?

Dr. Regelson: The Lissoni study abrogates that objection on my part. Melatonin has tremendous virtue. It's also an upregulator of immune responsiveness. DHEA has the same potential. There is now a study of cancer prevention organized by the National Cancer Institute looking at DHEA. DHEA not only may have a role in protecting against the development of cancer, but also, by inhibiting the pentose shunt, it has inhibiting effects on DNA synthesis. We studied it ten years ago. Unfortunately we were never able to develop the numbers, and my

political situation did not allow me to pursue it. But DHEA also should be looked at as an antitumor agent.

Of course, these are over-the-counter. I'm a little concerned. I would love to see physicians involved with so-called food additives, and certainly DHEA and melatonin are both hormones. But that's the way things have led. Again, relevant to the anti-aging potential for DHEA, that's an individual decision. Based on the literature and my own experience these are safe hormones, but it's better if you have a doctor look after you. I've been on DHEA for 15 years. I'm trying to save my rear.

Dr. Richardson: I'd like to go back for a moment to the antiangiogenesis issue and inquire as to your opinion and anyone else's opinion as to what's happening. Why are the available compounds not in use?

Dr. Regelson: It may be commercial. I don't think it's Folkman's fault. He's seeking to isolate the active compound, and heparin ...

Dr. Richardson: Let me mention parenthetically that Folkman does not own any stock in Antremed.

Dr. Regelson: He doesn't have any stock in Antremed. I feel sorry for him. He should. That's interesting that he doesn't. It's nice to know that he doesn't, in a way. But I would buy the stock. My attitude would be totally different.

The point I want to make is that I don't know why this has been ignored, particularly now that we have a much safer heparin available. It may have some of the same properties of the heparin-like compounds that I looked at 40 years ago. You can give these steroids IP without any problems, apart from giving them systemically by the standard IV route, or IM route, for that matter. I don't understand it. We have blind spots, certainly this work in regard to heparin and curing cancer with angiogenesis inhibition.

It could go the other way, incidentally, because it interacts with f-trophoblastic growth factor to stimulate angiogenesis. You need the corticosteroids on board that have this blocking action. Why somebody hasn't renewed that and made an issue of it, I don't know. I think people have forgotten, with all the publicity with regard to angiostatin. The dextrin 2-sulphate that is being looked at at Hammersmith is producing remissions in Kaposi's sarcoma. It may have antiangiogenic activity in its own right.

Panelist: The pharmaceutical companies are saying that they don't know how to set up the standards to look at angiogenesis materials.

Dr. Jonas: Any comments on that?

Dr. Regelson: I'm surprised that they can't develop standards because corneal vascularization is a very good model for *in vitro* assay. There's also the egg yolk sac assay. There are a number of assays for angiogenesis, so I don't know what the problem is with standardization. It doesn't make sense to me. But again, I don't know why people have forgotten the heparin steroid story.

Dr. Richardson: Actually there are a number of antiangiogenic agents out. At M.D. Anderson they're testing the TNP 470. It's not as promising as before. We just had several groups that have synthesized products from shark cartilage present, and some of those are moving right into phase I and II trials. A number of these agents are in the clinical test sites now.

Panelist: Dr. Regelson, you mentioned earlier that combination things in many cases may be more effective, or theoretically they might be more effective. One of the claims for shark cartilage is that it has antiangiogenesis effects and that there are multiple factors in it that produce those effects. I wonder if any of the panel members might want to comment on that design issue, of looking at the whole product, or waiting to isolate the specific active ingredients that might be causing those effects, realizing that there are others who claim that cartilage works by different mechanisms than antiangiogenesis. Perhaps that's not a good illustration. It's the same issue that comes up in many herbal products, in which there are multiple components and they probably have multiple effects even on the same clinical condition.

Dr. Regelson: I can give you another illustration of this. It's again a sad part of my life. I could never get it moving and it still is a dead issue. The group in neurosurgery at the medical college and I became interested in the fact that when you have glioblastoma and you grow glioblastoma cells in tissue culture, for a normal individual your buffy coat can interact to kill your glioblastoma cells in culture. But the individual with glioblastoma was paralyzed in that regard. You would not get the cell killing effect against the glioblastoma target.

We had a very primitive cell separator, and we skimmed off the peripheral lymphocytes from patients with glioblastoma. Then, through the craniotomy and through a catheter, we infused the patient's own lymphocytes into the tumor bed. The idea was that if we got enough lymphocytes in there maybe we would get an endogenous effect like TAL, tumor associated lymphocytes. In those days we didn't know anything about TALs. We forced lymphocytes into the site and we got tumor regression. But it turned out that when we got an Aminco cell separator, which was a fancier separator that gave us a 90% pure lymphocyte population, we got totally negative results.

Looking back at this, it occurred to me that the reason we got success with the more primitive instrument was that it was contaminated by 50% polymorphonuclear leukocytes. It was a 50-50 split. I raised the question, is it possible you can't use pure lymphocytes, that you need a triggering effect of your polys or your macrophages to interact with your lymphocytes to get the effect? I couldn't convince my colleagues to do this, and the whole thing died. It's reported as a negative study. Yet the initial study using a mixture gave us a positive result. What are you going to do? If you don't have control of your patient population, essentially as a clinician the essential feature is what Stalin said about the Pope. How many troops can he mobilize? The question is, can I mobilize troops? If I can't mobilize troops I can't do the studies.

Dr. Jonas: Thank you. That's a great illustration of the complexity that needs to be assessed in looking at the details. To make broad claims without assessing the details often doesn't help us or move us forward very much. I'd like to open it up now to the audience.

Please go to the microphone. Also, please limit your comments to specific questions or short comments so that we have a chance to have a dialogue. Thank you.

Participant: My question is to the panel at large. I'm a surgical oncologist and I come from Legacy Cancer Services in Portland, Oregon. We've been looking at doing research in complementary therapy and trying to figure out how to bring complementary therapy so that we can offer it to our patients. In looking at setting up a study we decided to go with something fairly small that we could handle. It's looking at control of hot flashes and symptoms of menopause in breast cancer patients.

We are struggling with a couple of things. One is getting our research proposal through the investigational research board, the IRB, and having naturopaths who are not on the medical staff and trying to figure out how to do that. How did you do that with your studies, especially as relates to melatonin? How did you deal with it? The other is the question of the placebo effect. The naturopaths we're working with are really concerned about how to control for that. Do you have suggestions?

Dr. Richardson: Our study with melatonin is a little different. What are you going to be using to treat the patients with?

Participant: Vitamin E, soy, and possibly black cohosh.

Dr. Richardson: Is it going to be individualized, or is it going to be a multifaceted treatment that's going to be the same for everybody that gets it?

Participant: We're going to be comparing standard therapy, which usually is bellergal or clonidine, versus complementary therapy, which would include vitamin E, soy and possibly black cohosh.

Dr. Richardson: But it would be this therapeutic regimen?

Participant: Right. Practice standard versus practice standard.

Dr. Richardson: With the melatonin we're using a fixed dosage. We've gotten an IND, and it will be administered in the pharmacy. We're not having anybody outside deliver this. It's going to be administered by the oncologist in a randomized fashion. It's the cleanest approach. As far as the placebo, we asked our oncologist about that. She said it's very difficult, especially with cancer patients, to withhold a treatment. So we aren't going to have a placebo control group. It will be compared with standard care, and that's fine. You're comparing it with an active, or sometimes it can be an add-on.

Panelist: You can work with people in the IRB. There are individuals in that group who will help you prepare your documentation to satisfy their needs. You could try that.

Dr. Richardson: But that's a do-able study. That's no problem. We can talk later.

Panelist: The only question that I have is that you have a naturopath who is interacting on your IRB. The question is, in your patient population do you have believers and nonbelievers? It would be very interesting to dissect out those who would go to a naturopath versus those who would not, particularly if you have some kind of natural therapy as part of what you're doing.

Dr. Cassileth: Ideally you have another arm of the study in which patients are given the same alternative treatment not by a naturopath, or patients are given just some time with the naturopath, so you can compare that influence.

Dr. Beuth: We have made quite some studies on quality of life and on outcome of complementary medicine. We always face the argument that it might be a placebo effect. We came to the conclusion that we don't make any study any more in Germany without a placebo control, even if it is very difficult to establish. We are doing our studies now always with a placebo control. That might be the most proper way to exclude side effects which are not related to the treatment you give.

Dr. Jonas: Do you have any recruitment problems for those types of studies though?

Beuth: Yes. Yes.

Dr. Jonas: It's difficult sometimes to get patients to enroll in studies.

Dr. Regelson: In regard to placebo control, it's important that the placebo be tinged with the aura of a therapy. I always felt that if you're going to give a placebo and you're comparing it to a standard therapy that makes somebody a little sick, the placebo should also make the individual sick at the same level.

To give you an example of how important these things are from the point of view of marketing, I know a consultant to an over-the-counter company that was coming up with a caffeine no-doze product for driving your truck or your car at night. Caffeine is supposed to help you stay awake, right? The trouble with caffeine is that it doesn't give you a rush the way an amphetamine does. So he put a little niacin in there to produce the flush. Now that you flush, you know it's working. That's something that we should keep in mind from the point of view of placebo effect.

Dr. Jonas: That type of thing hasn't been looked at so much in cancer, but clearly in the psychotherapeutic and the depression literature they've done studies looking at active placebo, as those are often called. You do get higher effect rates from active placebo, sometimes making it even more difficult to tell the difference from your active treatment.

Participant: Dr. Cassileth, before going to your article, looking at it and studying it, I want to be sure I understand something you said. At the end, when you showed the two lines overlapping between the group that received the alternative therapy and the group that did not receive the alternative therapy, you said there were two ways to interpret that overlap. You said one was that the group that received the alternative therapy did no worse than the group that received conventional therapy. Then you said something that I don't quite understand. You said

the other way to interpret it is that the group that received conventional therapy did no better than the group that received alternative. I thought you said at the beginning that they both received standard therapy.

Dr. Cassileth: They had received standard therapy, but the experimental group in this case had also received the full regimen of the alternative clinic. It was that regimen that was being tested. The results were that there was no difference in survival time between the two groups. I made that point because many people said, "See, the alternative therapy didn't do anything." What I'm saying is you can turn it around and say, "The mainstream therapy didn't do any better than the alternative."

Participant: But I thought they both got mainstream therapy.

Dr. Cassileth: They did, but the claim of the alternative therapy that we were studying was that it would improve the situation, that patients would get better to some degree if patients believed this.

Participant: I have a brief comment on Dr. Cassileth's study and then a quick question. I thought it was a terrific study. If your interpretation is right about the quality of life being a result of high expectations, that's a really important finding and suggests that alternative practitioners have to find a way to engender hope without illusions. That's a critical issue for alternative therapy practitioners and for research.

The other question I have has to do with the fact that antioxidants are being used by cancer patients all the time, be they vitamins, minerals, hormones, enzymes. My question to perhaps Dr. Regelson or all of you is the question I hear most from cancer patients. What about using them in tandem with chemotherapy? To what extent do most classes of chemotherapy depend on some pro-oxidant effect for their efficaciousness? And to what extent is it a possible hindrance to be using high-dose antioxidants at the same time that people are doing chemotherapy? Does it depend on the class of the chemotherapy, the mechanism of action of the chemotherapy? Is it a generality that it's a problem, or is it a generality that it's not problem?

Dr. Beuth: I remember a big study by Kedar Prasad in Denver. He checked the effect of antioxidative vitamins or trace elements on the proliferation capacity of tumor cells, on the influence or the interaction of chemotherapeutic agents and proliferation. He found there was no effect. Even if he employed high concentrations of vitamins and trace elements, they didn't inhibit the activity of the chemotherapy. He checked about 10 to 15 different chemotherapies. But these were in vitro studies and it's very difficult to interpret it and to give it into the macroorganism.

Dr. Jonas: That's an excellent question. You can also extend it. It appears more and more patients are using over-the-counter supplements, herbs etc. that do have or can have fairly significant pharmacological effects. The drug supplement interaction is one example of a major issue that we know very little about in many cases.

Panelist: There are even some studies suggesting synergy, that antioxidant vitamins may actually enhance the efficacy of certain types of chemo. It's a very confusing area.

Dr. Richardson: That is something that we're very interested in, especially one of the antioxidants, CoQ₁₀. We've done some preliminary *in vitro* studies testing it with a various range of chemotherapeutic regimens as well as protease inhibitors and those sorts of things. We have found that at nontoxic doses it's neither inhibiting or boosting the effects. That's an area we're very interested in. It needs a lot of work.

Dr. Regelson: Again, it depends on the compound. I certainly wouldn't want to administer an antioxidant simultaneous with anthracyclines, or perhaps a nitrosourea or some of those compounds. But later on, I don't know what the half-lives are, but it's very interesting. A colleague of mine has developed ribo-nucleotide reductase inhibitors that are also very potent antioxidants and are very useful in preventing reperfusion injury, which is a pro-oxidant recirculatory event. It may very well be that in combination we could get a double whammy when a compound like that may be available. They're coming up on the outside in the next year or two.

Participant: I have a question about research design, specifically related to the study of breast cancer. It seems that one of the major failings with chemotherapy is that we don't know exactly who it helps. I wonder to what extent in the selection of patient sample or in the stratification of a patient sample there is attention being given to looking at all kinds of indicators. To what extent are pathology and prognosis and the various indicators that either

exist now and may come up later even – to what extent, for example, are nuclear grade and estrogen receptor status and all of these things taken into account? This would be so that when we look back we can see something about the differentiation in the group that was studied that's a little more discrete than we now can see.

Dr. Cassileth: The factors that you mention such as ER receptor status are routinely included in all breast cancer studies.

Participant: I have one quick question then with respect to the Bonadonna study, the 20 year study of chemotherapy on metastatic breast cancer. I understand that nuclear grade was not even a component of that study. Does anyone know?

Dr. Regelson: Certainly in relation to head and neck cancer, if you're not immunologically responsive to standard skin antigens, you're dead. There are prognostic features that relate to host response, but whether they are things that are pathologically useful criteria, I don't know. There are number of them out there, including cathepsin assays and things of this sort.

I had a debate over drinks last night with a colleague who believes in *in vitro* screening. You take tumor cells from a patient and you subject them to a screening in an effort to determine which anticancer drug may kill your tumor cells. Similarly, the nude mouse is now the big criteria for chemotherapeutic effectiveness. You take a human tumor and put it in a nude mouse. If it inhibits the human tumor it's much better than if it just inhibits syngeneic mouse tumor. I personally think that's all nonsense, but apparently it's still blurbly around. Back in the early

80's every mother's sister's uncle's cousin set up a little laboratory to do *in vitro* chemotherapy testing to try to predict which drugs were going to work. My experience was that it was worthless. But this guy last night told me over drinks it's great stuff. I don't know.

Participant: I have two quick questions. In conventional medicine many patients aren't disclosing to their physicians that they're on alternative treatments, and this could skew the results of conventional medicine clinical trials. How is this taken into consideration in research on alternative medicine, in terms of usage of other complementary and alternative techniques and how this would influence the results?

Dr. Cassileth: I'll try to answer that. Years ago when I was at the University of Pennsylvania, my group did the first national survey of cancer patients to find out what they were doing in terms of alternative medicine. We did a careful job, and many other studies since that time have failed to take into account the kinds of issues that you're raising. We asked for every single therapy that the patient was using. We had all that information. That was all analyzed. Many surveys of that kind that are done today fail to do that. It's a major methodologic flaw.

Dr. Regelson: I'm not doing primary care any more. I've reached that age that I don't have to worry. I do consulting practice, but I'm not one-on-one in the day-to-day care of a patient. When I used to have patients and did chemotherapy, over 20-25 a day in a busy practice, my patients related to me. I asked them, "What are you taking? What are you doing?" It's a one-on-one interface. If you're not close to your patient you may not find information like

that. After all, I'm the witch doctor. You have to trust my power as your placebo effect or your alternative medicine. It's equally as important to what you're taking.

Panelist: But it depends on who is asking the question. If you're in a research setting, it's usually not the MD, and patients are usually very open. However, the new data that have come out from New Landmark Study I think it's called indicate that most patients today in fact do tell their physicians what they're taking.

Dr. Jonas: There's a complication on that. They did a survey at the NIH clinical center to look at herbal treatments. It was to find out how many of the patients in the clinical center, all of whom were enrolled in some type of study, were actually using herbal treatment. It was in the area of 16%. They were only looking at herbal treatments. They presented a number of cases illustrating that patients were very reluctant to talk about those therapies because they were afraid they would get bumped off of the trial. Either of those scenarios is not good, obviously. To not say what's going on, if it has potential interactive effects, is not good. On the other hand, if people are doing that and it does in fact have an effect on the trial, then it potentially could compromise the results of the trials.

Dr. Cassileth: But that's a methodologic issue that can be controlled.

Dr. Jonas: It is. Absolutely. Making sure that mainstream researchers and practitioners are aware of and are beginning to discuss and know how to talk with their patients about this is an important aspect of making sure that this communication gap gets closed.

Participant: Thank you. Just one other quick question. What do you all see as the future of possible regulation of quality of herbal and natural remedies?

Dr. Jonas: That is not a quick question. I'm going to ask if we could skip that. If you want to come up and talk to some of us afterwards I'd appreciate it.

Participant: My name is Michael Hall. I work with Dr. Dean Ornish. I'm the assistant project director on a prostate cancer study that he's conducting. We're basically applying the same model that he used with his heart research for the prostate cancer study. Everyone who is eligible and wants to join signs an informed consent, so the control group are pretty much aware of what we're asking the treatment group to do. We have a lot of control group patients actually implementing a lot of these changes.

I hear, and I'm hoping you can tell me how true this is, that there's a bias in the research world to weighting the primary analysis, the between-group difference, more heavily than the secondary analysis, which is the relationship between, the dose-response relationship, adherence and outcome. Could you speak to that? My concern is that if this is effective and we do show a dose-response relationship, the control group patients who are making these changes and getting better will minimize the between-group difference.

Dr. Cassileth: That was a very common problem early on in AIDS treatment. Very savvy patients would trade drugs on the street, so that patients who were in experimental trials, who were the control group, were in fact getting the experimental treatment. This plagued

researchers. It is a very common problem. It's not surprising that it happens in your situation. You have to prepare for that in advance. Accrue twice as many patients as you think you need. Then eliminate all those who decide to go on a special diet because they heard that the experimental group is doing that and it sounds really good. It happens all the time.

Dr. Jonas: On the other hand, that eliminates your intention to treat analysis which some people say then is invalid. This is a problem in these areas. The results of the Mr. FIT study, for example, were practically undermined because the patients were aware that diet and lifestyle were important and the control groups began to do this.

We're now planning a study on shark cartilage. In addition to the product issues and all the other things that we've talked about, outcome measures, one question that has come up is the whole issue that patients are using it. Cancer patients especially are using it quite extensively. If we are seen as studying it in some way because we're trying to get data on it, what is going to prevent those who get randomized to be in the control group from going out and saying, "I'm going to take it just in case." They would be getting a product for which we have no idea what the quality, quantity, etc., is. It can be a major problem. It can completely undermine the results of a study if it's not controlled.

Dr. Cassileth: That can be well controlled because you can use a placebo.

Panelist: You can use a placebo, but that doesn't prevent anybody saying, "I have a 50% chance of not being on it. I'm going to hedge my bets."

Dr. Cassileth: And going to the store and buying it, getting double the amount.

Dr. Jonas: Exactly. To enter into a clinical study is to say that I'm essentially willing and volunteering to be a test subject. That means I'm entering into this because I'm willing to essentially take a risk that I'm not going to get something or going to get something in order to advance our knowledge. If someone is not willing to do that, then they shouldn't be entered into the study. That should be built into the informed consent up front.

Panelist: You'd probably have nobody join the study.

Dr. Jonas: That could interfere in many cases with recruitment efforts. That's right.

Dr. Richardson: That's why we have probably 3% of the cancer patients enrolled in clinical trials.

Dr. Jonas: Already we have a very small percent, even in conventional medicine.

Participant: My understanding is that the primary analysis is the most important. But in my opinion the kind of intervention that we're doing is qualitatively different than, for example, giving somebody a drug versus a placebo. In that case, I can understand why the primary analysis would be most important. But if there is a clear relationship between adherence to the program and outcome, and if that were to be ignored because of crossover between groups, I think that would be a disservice.

Panelist: I agree. I'm not saying you shouldn't do a secondary analysis on it if you have the data that allows you to do that. But for a lot of what we're talking about here, frequently the data is not collected.

Panelist: You're dealing with a dietary study, right?

Participant: A quarter of it is dietary, yes.

Panelist: Can't you monitor the results of the diet?

Participant: We're doing a secondary analysis. I just mean that in terms of having it evaluated and accepted as statistically significant, that would be overlooked because of the between-group difference not being there. It's intrinsic to the study design that we're going to have people in the control group making changes, which wouldn't be true if we had a particular drug and a placebo.

Panelist: You might talk with people who were involved in studies with similar problems, like people who worked on the Viagra trial. That ended early.

Panelist: Yes. Addressing the statistical issue, which is essentially what you're talking about, up front is very important.

Participant: My name is Libuse Gilka. I'm a physician. I would like to turn attention to some additional factors which can play a role in the final results of anything that is given to the patient. I would like to ask here about the possibility of looking into the factors which can play a role in modifying the results of whatever medication. This is based on the presentation at the World Conference on Breast Cancer by a group of exceptional survivors.

It is an observation which was made on the basis of the interviews of the physician who traveled sometimes more than half a century ago around the world to interview every person who had medically documented so-called spontaneous disappearance of cancer. He found that in every case where there was this so-called spontaneous remission of cancer, in every patient there were the same four conditions.

Number one, they changed their lifestyle. They stopped drinking. They stopped smoking. They started to eat raw food, mainly vegetarian and fruit, meat free. Secondly they decided to forgive everyone, including themselves, and repaired all the strained relationships which they may have. Thirdly, all of them claimed that they were absolutely sure from the beginning, that they had absolute faith that they will be healed. It was connected with a lot of prayer, they said. Number four, all of them made an inner commitment to whatever was for them the expectation of God, what they will offer for this gift of life. They started to work on this issue, for which they did not expect any kind of reward otherwise, immediately while they were still ill. On the basis of that, then the group of these so-called exceptional patients who presented that paper was looking at that. It looks that when these four factors ...

Dr. Jonas: Excuse me. We're going to have to close up here. Do you have a question for the panel?

Participant: I do have a question. Is there any questionnaire which we can use to assess these factors?

Dr. Cassileth: You have given a perfect example of the need for proper prospective controlled research. How many patients have we all worked with who changed their diet, who prayed, who wanted desperately to get well, and who died? They're not included in this kind of analysis.

The second point is a very important one. I did not hear Dr. Siegel's presentation, but I suspect he did not offer to you any slides on the one study that was done of his patients. It was reported in the *Journal of Clinical Oncology*. George Gellert is the first author and Dr. Siegel is the last author. In that study, in which they looked at the ECAP patients and compared them to a group of similar breast cancer patients who were not in Dr. Siegel's program, they found no differences in survival.

Participant: I agree with you. I was on his presentation already on the previous conference. I spoke with him personally. The difference here was that all of these four factors were present in every patient.

Dr. Cassileth: You're raising two separate issues. That second issue has to do with the importance of proper methodology to understand what's going on.

Dr. Jonas: I've been told we do need to stop now, because they need to break the room down. We started with spontaneous remissions and remarkable recoveries and we ended with that. Tomorrow we will continue the discussion. I'm sure some of these issues will still come up. Prof. Beuth, Dr. Mary Ann Richardson and also Michael Hawkins from the Lombardi Center will be here to continue the discussion. I want to thank all our panel members who participated today, and thank you.