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Diet and Cancer: New Approaches to Ancient Remedies

The question I'm going to work with tonite is what does one do in terms of nutrition to forestall further development of prostate cancer (pc)? Because some people are at risk, some already have the disease, and everyone knows someone who has it. With men, I sometimes say that pc is really the type of thing, it isn't "if", it's "when", b/c nearly every man will develop pc at some time during his life. If you took a group of 80 yr. old men who'd been in automobile accidents and looked at their prostates, you'd see that the great majority of them have some evidence of pc. So the question really is how do we intervene so that if you don't have the disease, you don't get it, and if you do get, you try to keep it under control and what does diet and nutriition have to offer and that's what I thought I'd tackle tonite…what there is that we can all do about it. I might say too that the trouble with nutrition as a field is that is has too many experts. Everyone who's lost more than a lb. or knows someone who's lost more than a lb. is an expert in nutrition and you can listen to the radio and tv and hear all sorts of experts. Yet the more we study nutrition the more complicated we get to see it.

As a resident I heard a wonderful lecture by a man who was advertised as the world's authority on the lymphocyte. As he began his talk, he said the more I learn about lymphocytes, the less I understand them. I think that in many ways that's really the story here. We have many experts and I'm always concerned with someone who says he has all the answers b/c we are still striving. This is a new field and there are constant developments every day. Before I give a talk, the last thing I do is look at the newspaper for what's going on b/c it's a tremendously important field and there's a lot going on. One on the problems is that our friends in the media, and I love them dearly, but whenever there's a new study, they act as if this is the word and 100 yrs. of science is out the window. One of things that one really does need to do is put all these new findings in perspective.

With respect to pc and nutrition, I think it's important that recommendations that we make recognize the totality of evidence.

Before I discuss the specifics, I'd run through with you what types of evidence are available and what these contribute.

The first type of evidence is Basic Science. In basic science, one looks at cell-free preparations, one looks at sub-microscopic levels. People work very hard on basic science mechanisms. The value that this has is that it establishes a mechanism, it says how something works. Many people say it doesn't really matter unless it's done in humans but really these basic

science studies are very helpful in telling us how science really works, how the body works.
So the first type of evidence is in basic science, essentially cell free systems.

The second type of evidence is with animal models. In animals you can transplant human cancers. You can take the cancer and put it into an animal and see what effects it, what inhibits it, what stimulates it.
You really learn a great deal with the work in animal models. You may have heard the term "nude mouse". A "nude mouse" is not one that doesn't go around wearing any clothing. A nude mouse is one that doesn't have the capacity to respond to foreign anitgens. The animal is treated in such a way. The nude mouse is a very helpful model to study the transplanted human tumors, so what one sees in an animal is really very helpful.

The third type of evidence is with case control cohort or epidemiological studies. This means you take a population and you follow them for a period of time or you look at a population and how they're eating and then you look at what happens to this population over time. What is really particularly valuable is to look at a population that moves. For example, there are some elegant studies that have been done about the Japanese who have moved to America. They acquire the American pattern of disease. In fact, the former director of the American Health Foundation said in one lecture that he gave, the Japanese are killing us with the balance of trade but we're getting even – we're killing them with our food. There's really a lot to be said for that.

But you learn a great deal from looking at a population and what they do. And a case control or cohort study is a population. The epidemiologists are the ones who study huge populations. They act as if they have the word and whatever anyone else is doing is just playing. But really they have a place but it's not the only place.

The final type of evidence is the double-blind placebo controlled trial. This is very relevant to prostate cancer and I'll get to that, because there was one study that was done that did more to set back nutrition and prostate cancer than anything else. The idea that double-blind placebo controlled trials are the ultimate answer is not true. They have their own problems. In addition to that, they are enormously expensive. The major trials have cost more than $100 million to do, some more than that. With money the way it is these days, it's unlikely that another study will be mounted unless there is evidence from all of these types and the evidence is congruent – meaning it all comes out to the same conclusion. I feel myself that each of these types of information is most valuable.

The double-blind placebo controlled trial is a valuable thing to do but it has it's own problems. Of course it requires compliance by patients, it requires multi-institutions, sometimes multi-countries, and you have to be sure that the thing is done the same in all these places.

I think the best evidence for why these studies may not work comes from a double-blind placebo controlled trial that was done in Scotland recently. This information was given to me by the late Dr. David Kurchefsky, who was the chairman of our extenal advisory board, a very great scientist in Philadelphia. I understood the people who designed this trial of a new drug

made great efforts to be sure that the placebo was really well matched to the drug so that the patients would not know what it is and the investigators would not know what it is. So one day, as the story is told, this chap came in for his regular follow-up and I understand the conversation went something like this.."Bill, my good man, how are you today?" "Well, doc, to be perfectly frank, I'm exactly the same as when I first started with you. I'm no better, ah, but then again I'm no worse either." The investigator is thinking, well, that's ok, he's probably on the placebo, he's been on a few weeks. And then the patient turned to the doctor and said, "Oh, but doc, you tried to pull a fast one on me, didn't you." The doctor said "what do mean by that?" "Well, doc, you switched the pills on me." The doctor was just thunderstruck how anyone could figure this out. He said, "Did they taste different to you? Did they smell different to you?" "Oh no, doc, nothing at all like that doc. When I took your first set of pills and threw them all in the loo, they floated. This time when I took all your pills and threw them in the loo, they sank to the bottom, the very bottom."

So you know these tests all depend on the patient taking the thing. So the point really is these may be considered definitive by those who do it but really it leaves a lot to be desired.

But the main thing I'm trying to give you is some feel for the fact that these things are not easy to do and the conclusions are often very difficult to come by.

Now let's look at what is known in relation to nutrition and the prostate. In preparation for the meeting tonite, I really made a very thorough study of all of the work that has been going on with these 4 types of evidence to see what is really new and what has stood the test of time. The first thing I would talk about is **vitamin A or retinol**. Vitamin A as you know is essential for vision, it's essential in the brain, it's essential for cellular growth. One curious thing about this is that it is also converted from it's precursors. So vitamin A itself, the deficiency of vitamin A itself is very widespread throughout the world. In fact it is believed that serious cases of diarrhea and malaria are often associated with deficiencies of Vit. A. But if you take too much vit. A, that can be toxic. So you have to go a line between what is safe and what is toxic.

The thing that is really quite fascinating and one really new development in this area, is the finding that the higher levels of vit. A are associated with less aggressive pc. It's not clear that there is more pc when there is less vit. A. That I think is still unclear. But what I think is very clear is that the high levels of vit. A seem to do some protection against the aggressiveness of pc. This is a very new finding that has just come out this year. The question is, if this is confirmed and extended, it would suggest that maintaining vit. A status is an impt. part of keeping the disease from becoming aggressive. Many of us are excited about the opportunities to intervene in pc b/c it has such a long interval between the first abnormalities in the cell and the development of fulminant disease. That suggests many ways to intervene – to intervene early, and during the course, and not to give up once the person has cancer.

That's an impt. point, that once you have pc, efforts at prevention and tx should not stop b/c now you want to make the disease less aggressive.

The biggest problem in pc, in terms of manipulation, as I see it, is that in time the hormone sensitive pcs lose their sensitivity to hormones so that early in the course of the disease, men with pc respond to endocrine manipulations, such as blocking the release of hormones, taking anti-hormones, so to speak. Interfering with the androgen or the male hormone production or action is very helpful early in the disease. The problem is that late in the disease it doesn't respond to this. We don't really know what is the signal that makes the tumor suddenly lose it's hormone responsiveness. But the point really is that you want to be able to prevent the disease from becoming aggressive. I would say this is one very impt. study that suggests that keeping enough vit. A in the body so that the levels do not become deficient and are higher than others is a very good way to do this.

So how do you do this? Well, it's no secret that vit. A comes from a large number of animal sources, and it's precursor, beta-carotene, comes from vegetable and fruit sources. So it is said that the retinoids – the term retinoid means that the substance can go into forming vit. A, and beta-carotene is again one of the ways in which one can have large amts. of vit. A. Really the best way to do that is to take a diet that's high in vegetables and fruits. It's fascinating that we're aiming now to have a diet that is similar to what the diet was at the turn of the century. At the turn of the century, people lived more on farms than they do now, they ate fresh produce.

All the evidence is that vit. A and other vits. can be consumed in large and quite adequate amounts thru the diet. Some people have said you should never take dietary supplements. I don't think that's good advice. I think the impt. thing is to realize is that dietary supps. are no substitute for a good diet. Some people think they can just take a pill and that makes for adequacy. No! The idea is that you have to take fruits and vegetables. In fact, each day new benefits of fruits and vegetables are discovered. They have a large number of agents and we are really just beginning to discover them so taking a pill is only going to give you a certain amount. It is possible that the next generation of supplements will contain substances from fruits and vegs. but right now you'd really do very well by eating a diet that's high in fruits and vegs. By that I do not mean fried potatoes or potato chips which are very high in fat and very high in calories and it's really a big problem. So I think that pills are not necessarily terrible but they have their place. It's interesting that the American Dietetic Assoc. which is a very large, powerful organization composed of dieticians, has been unalterably opposed to the use of supplements but within the past few yrs., they have come around to understanding that in some circumstances when the diet is not adequate, that you have to add supplements.

So I think that the issue about vit. A is very intriguing and it's not really ready for prime time but I think you should really keep an eye on this.

In my opinion the nutrient that really is ready for prime time both in terms of prevention and in terms of advanced disease is **vit. D**. This is getting a lot of attention these days and it should. B/c vit. D, we all know

you get this from sunshine and the first question anyone asks is, "sure I get it from sunshine but I don't want to get skin cancer. So what is a fellow supposed to do?" The answer is very simple, you just expose your skin on the face and hands for 20 min./day and you can absorb all the vit. D you need that will be powered by the sun. You don't have to go to the beach and put on a bikini and lie down for 8 hrs. – that is how you'll get skin cancer. So if you put on sunscreen, will that block the effect of vit. D? Yes, yes it will. So how do you handles this? "My skin dr. says I can't go out in the sun unless I put on a sunblock and my other dr. says I can't do that, I need the vit. D. What am I supposed to do?" The answer is you go out for 20 min. that's in small amounts and expose the skin and then you put on the sunblock. You also put on the sunblock repeatedly, you don't just put it on once. So it is perfectly possible to eat adequate amounts of vit. D in the diet and also make it from the skin without running the risk of getting skin cancer.

The other thing too is the risk of getting cancer, particularly pc, is related to the vit. D level in the blood. When you go to have vit. D measured, it occurs in several different forms. There is 25-D which is the first form that is made as the result of the precursor, the sunlight, and it goes to form this 25-D. 25-D in blood is an excellent marker for vit. D nutrition. So if you are measuring the vit. D in blood, that can tell you if you're getting in an adequate amount from skin or from diet. These days there's fortified milk, vit. D that's added to many foods, there's vit. D that's taken as a supplement. Vit. D is very important.

We all think of vit. D in terms of absorbing calcium from the intestinal tract and bone but vit. D has many more roles than that. One of the impt. roles of vit. D is to cause differentiation. That means that if a cell is primitive, and it has enough vit. D, it will become altered in the direction of a finished product – that is to say the likelihood of a cell becoming malignant is greatly reduced if there is more differentiation. The less differentiated a tumor is, the more aggressive it is. So we're looking for those tumors that are going to be controlled by a differentiating stimulus and **25-vit. D** is a differentiating stimulus.

Vit D is also converted into **125-D**. 125-D is really the hormonal form of the vitamin and that's the form that is effecting calcium metabolism and effecting so many of these other things. I think it's really very impt. to realize that vit. D is vital in controlling cancer growth. There now are a very convincing number of studies that show that vit. D will result in a less aggressive tumor. It will reduce the start and it will also reduce the severity once the disease has started. Much of the work on vit. D has been learned from animal models.

There is one cell type called the LNCaP cell, which stands for lymph node cancer of the prostate. This is a lymph node taken out of a pt. who had prostate cancer and it has been grown over the generations. It's a very good experimental model b/c it has many of the features of prostate cancer in the living person, mainly it makes PSA. It is sensitive to androgen stimulation. So when you take a LNCaP cell and you transplant it into an animal or you

grow it in a cell culture, how it responds is a very good indication of what is going on in the living human being.

It's been shown clearly that in the LNCaP and in patients, vit. D will have an anti-pc effect. It does this by several mechanisms. One is called apoptosis – which means premature cell death. This occurs normally and when it is accelerated, then you really have an objective where the cells have died quickly. This can be good or bad depending upon the circumstances. It has been shown that vit. D will cause apoptosis among pc cells. So one of the ways in which this acts is by causing premature cell death.

Another way in which it acts is by interfering with the cell progression in reproduction. We've all learned in school how the cells have mitosis and it goes thru all these different steps. The thing that vit. D does is that it halts the progression. The cells accumlate in one phase. So if the cells cannot progress all the way, they're going to die or they're not going to reproduce.

So what Vit. D is doing is causing premature cell death, it's causing differntiation - that means it's taking cells that haven't decided what they're going to do to go towards a mature cell and not a cancerous cell, and it's causing cell death, and it's also interfering with the rate of cell progression. So I would say that the evidence of vit. D working in pc is very persuasive. I think that we should all maintain an adequate intake of vit. D.

It is also thought that in pts. who have existing pc, the rate of increase of PSA is slowed by vit. D. As you know, whether the PSA is a good test or bad test for detecting pc, that's still debated, whether you should do screening and so forth. But there's no doubt that in any given individual the PSA change over time is extremely valuable. So what vit. D is doing is delaying the rise of the PSA with time. It is now thought that vit. D deficiency may promote pc and vit. D administration may slow it. So I would say that this is something we should all be doing – we should all be maintaining adequate intakes of vit. D.

I would say that vit. D meets the standard b/c the basic science work shows the mechanism, the animal models of human pc show efficacy, and the cohort studies and epidemiological studies also show this. There is not to my knowledge a full blown double-blind placebo controlled trial b/c the evidence is really very persuasive and these are just so expensive to run. So I would say that vit. D is an impt. part of maintaining prostate health. There's also some evidence that it can prevent BPH, benign prostatic hypertrophy.

The next nutrient that's been the subject of a lot of interest and I think justifiably so is **selenium**. Selenium, as you know is a metal, and it is found in the soil but the soil has different amounts of selenium in different parts of the country and in different parts of the world. In the US, there is a selenium belt in the southeastern part of the US, where the selenium in the soil is very, very low and if the selenium in the soil is low, it's going to be low in the plants that grow there. It's also been found that in New Zealand the selenium is also very low in the soil. The point is you don't know what is going to be present in what you eat, where it's from, but I think it's fair to say that eating things from various sources is really very impt.

So Selenium has been shown to have anti-cancer effects in animal models, in cell-free systems and in human epidemiological studies and also in trials. The difficulty with selenium is, there are several difficulties. One is that there is a very narrow range between efficacy and toxicity. Vit. B12 is an example of a dietary nutrient that you can take it till the cows come home and it won't do anything that is harmful but selenium is another story. If you take too much selenium, it has very real toxicity. The levels of 200-400 mcg. per day that are present in many supplements is perfectly safe but if you go 10x that, it's not a good idea. The point here is that selenium is very valuable as an anti-cancer agent.

The problem is this select trial which came out and it was published in the JAMA. It also illustrates the drawbacks to a double blind placebo controlled trial. This study showed that a combination of one form of selenium and vit. E did not protect against pc. This has done more to harm the effects of investigators in this field b/c the people who are really knowledgeable about selenium, I mean the people who work in the selenium field, all tell me that the type of selenium that was used is not as effective as other forms of selenium. When the study was being designed, several scientists wrote to NIH and urged them to use a different form and the people designing the study paid no attention to this. To those who know selenium, it's no surprise that there was a negative effect. Many people at NIH privately agree with this but no one wants to get up and criticize them. You know, it pays their salary. Many of the investigators are also unwilling to say how terrible it was to waste $100 million. They're afraid to say this b/c these people are going to be reviewing their grants and they don't want to insult the people who are going to be reviewing them.

We have literature that shows that there are forms of selenium that would have been more effective. Selenized yeast is among the most effective. This is sold is stores. Selenized yeast is believed to be the most effective form of selenium and that inorganic selenium is not as effective at all.

I think that there's a good case for studying selenium and this trial has thrown a great big wet blanket on the whole thing.

The next nutrient that I want to talk about is **lycopene**. No doubt you've all heard of lycopene. Lycopene is not a retinoid. A retinoid is a structure that goes on to form vit. A. Lycopene is a carotenoid. It has the same structure as beta-carotene and other carotenoids but it does not form vit. A. The thing that is fascinating about lycopene is that it is the single most effective anti-oxidant of the substances that have been found from fruits and vegetables. It is a very powerful anti-oxidant. For this reason, it has attracted a great deal of interest.

In addition to that, it has another quality which I think is very curious and perhaps very relevant. It seems to be attracted to the prostate. So if you look at the prostate both in humans and in experimental animals, the prostates will contain a great deal of lycopene. It seems to me that this is an impt. point b/c if you say that something is so wonderful but for some reason it doesn't get where it should be working, then what's the effect of it. But

lycopene goes to the prostate so to me there's a certain logic in focusing on this.

Tomato products contain large amounts of lycopene. The interesting thing is that with carrots and with tomatoes, processing, or cooking actually improves the health benefit. You know we all learn to eat raw fruits and vegetables but really with respect to tomatoes, it's tomato sauce, pasta sauce – all of these things are extremely valuable. In fact ketchup is actually a very rich source of lycopene. So it does appear that lycopene is another agent that would appear to be impt. in controlling the prostate, inhibiting the prostate, and preventing further growth. The controversy really deals with the fact that, is lycopene the only substance that effects pc, b/c many substances are in tomatoes.

It is shown now that consumption of foods that are rich in lycopene can reduce the risk of pc by 30-40%. As I mentioned with respect to carrots and with respect to tomatoes, and possibly others, the stewed or cooked varieties are healthier b/c the cell walls have been broken down and the substances are available. If you're having raw tomatoes, there's nothing wrong with that, but it's a good idea to have them with some oil, b/c that will improve the absorbtion of these healthy substances. So eating fresh fruits is ok – and tomato is really a fruit, not a vegetable, b/c it comes from a flower, and so forth – but the point is that if you take these vegetables and fruits in a stewed form, you're really doing yourself a service and it's not such a terrible thing. The point is really that the stewed and processed fruit is really probably in many ways more nutritious.

To conclude, I've tried in this overview to discuss some of the new things that are going on in the field. The essence is that there's a lot of excitement going on and you really do have to keep up with what's going on and to keep healthy, you really do have to follow the regular guidelines. So I wish you all good health, prosperity, and hope this is some food for thought or at least something to chew on.

Q & A:

1) With respect to the select study you mentioned, it said alpha vit. E had no effect but they neglected to include gamma vit. E. A Johns Hopkins article which preceded it said any study must include gamma vit. E b/c it's the one that's effective plus it activates the other two. Also a couple of weeks ago the American Association of Cancer Research talked about gamma Vit. E. I'd like to know what your opinion is on that.

Dr. R.: I think it's very true that vit. E, as you recall, comes in 8 different chemical forms, and if you're taking a vit. E supplement you really should take a vit. E supplement that has all of the different kinds. It is certainly true that there is much data in support of gamma tocopherol so rather than just 1 form of tocopherol you really should take a lot of them.

2) You talked about amounts and toxicity. Is there any way we can find out how many units of different foods – the bottom that's effective and the top that's toxic?

Dr. R.: That's a very good question. With respect to selenium, it is believed that taking 200-400 mcg. is effective and safe. It's when you go several times above that that you run into difficulty.

3) You talked about several nutrients that have a positive effect. Can you talk about one or two that are really negative, that we should avoid?

Dr. R.: That's a good question also. It is believed that saturated fat is a risk factor. In fact, obesity is a risk factor. Both saturated fat and obesity are believed to be risk factors.

4) Is there a reason for Vit. D3 rather than just vit. D?

Dr. R.: D3 is one of the active forms. It is a nutritional form of vit. D, if not the hormonal form. Vit. D3 is perfectly active and perfectly effective.

5) ----- Genistein?

Dr. R.: That's an interesting issue about soy. For women who are at risk for breast cancer, soy has been a real mess b/c you could argue that since soy has estrogenic effects, you shouldn't take it. You could also argue that although it has estrogenic effects, it has weak estrogenic effects and may block the powerful estrogens from binding to the receptor. So it can be argued both ways. But soy and genistein appear to be perfectly safe for men. So I would say that genistein does appear to be effective.

6) In the area of nutrition, as you said, ingestion of some of these nutrients can slow the growth of prostate cancer. But I've heard that with proper administration of dietary changes and so forth, you can eradicate the cancer that you have. Is that true?

Dr. R.: Well, that's tricky b/c it's certainly more accurate to speak in terms of slowing things down. Whether it can totally eradicate, I just don't know. Beware of those schemes that promise results that are unrealistic. I think if one is able to slow down the tumor so that it doesn't become symptomatic or more symptomatic, that's really quite an achievement, b/c pc will be found at autopsy in many, many individuals. The idea is to die with pc not of pc. So if you can slow it down, I think that's a very great achievement.

7) What is the latest thinking on Garlic?

Dr. R.: I deliberately didn't mention garlic b/c our laboratory has been working on garlic for many yrs. so I admit to a lack of objectivity on the subject but there is outstanding evidence that garlic inhibits pc. Those

people that take more garlic have less pc. There are studies that it's been shown in England and in Italy. In the experimental animals, this LNCaP cell that I referred to, garlic derivatives will absolutely knock it out. We think that garlic is a very important substance and that you really ought to be taking that.
To cut to the next question, as far as "what form of garlic do you recommend?", my answer is I don't do commercials.

8) Is it possible to get the list of citation about--- articles?

Dr. R.: Yes, I could do that. And the list now will be different in a yr. I'll get that list together.

9) How do we know amounts of Vit. D that have D3? Do numbers mean anything?

Dr. R.: Well, that was asked by one of your colleagues. D3 is a form of vit. D and that is certainly fine. It is really taking this in adequate amounts. Studies show that large numbers of Americans don't get in enough vit. D. 2 impt. points in this connection, as we get older, the skin loses its ability to make vit. D. One of the aspects of aging is that the skin loses its ability to make vit. D.
The other thing is it depends very much on race. We know that for some reason, black individuals are more susceptible to pc and it may run a more virulent course and the vit. D levels are often low in the black populations.

10) 2 questions: How effective is lycopene after pc? The other question is what is the most effective form of selenium?

Dr. R.: I can only say that selenized yeast appears to contain the highest amounts of selenium. In this connection with garlic, garlic is also a seleniferous plant. That means it is very effective at absorbing selenium in the soil. So those individuals who take garlic will also have higher selenium.

(and the Lycopene?) All the evidence would seem to suggest that you don't give up after the horse is stolen – what's the analogy? Lock the barn door after the horse is stolen? But you continue to do this.

(so even thought it's not going to the prostate anymore, it still can be effective? B/c you said lycopene tends to go to the prostate.) Yes, but that's not the only place it goes. The point is that there are many different substances in the diet. But Lycopene has this curious propensity to be accumulated in the prostate.

11) I understand that you are going thru the link between pc and nutrition. Is there anything you talked about today that's applicable to possible cancers, like breast cancer?

Dr. R.: No it isn't. Like I mentioned, soy… (yes, I understand about soy.) Well, I think breast cancer is certainly favored by controlling your diet. There are many other factors that effect if but in general, following a prudent diet is effective for all types of cancer.