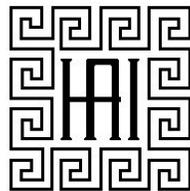


**DIVISION OF CANCER PREVENTION**  
**ORAL HISTORY PROJECT**

**SECOND INTERVIEW WITH**

**Dr. Peter Greenwald**

**DECEMBER 4, 2008**



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**National Cancer Institute  
Division of Cancer Prevention Oral History Project  
Interview with Peter Greenwald  
Conducted on December 4, 2008, by Victoria Harden**

**VH:** This is the second in a series of interviews with Dr. Peter Greenwald, the Director of the Division of Cancer Prevention, National Cancer Institute (NCI), about the history of his division, on December 4, 2008. The interviewer is Victoria Harden.

Dr. Greenwald, when we stopped the last time, you were explaining to me why Vince DeVita's [Vincent T. DeVita, M.D.] management style convinced you to leave New York for Bethesda when Arthur Upton's [Arthur C. Upton, M.D.] style did not. Would you begin this interview by describing Dr. DeVita as a physician, a scientist, administrator?

**PG:** Yes. Vince DeVita is a very strong scientist, particularly in the clinical area. He led in the development of therapies for Hodgkin's and other lymphomas. He also was a strong and dynamic leader in the sense that he would listen to input and act forcefully when necessary. He believed in openness and open advisory groups. He believed that unless you could convince an advisory group that this was a good direction, you might want to rethink the direction yourself. But at the same time, he would make decisions and follow through on them, both about people and about programs.

Art Upton is a very kind, wonderful scientist, but he didn't like to be in the midst of debates and turf wars, and such things, which were part of his job as NCI director. I was coming into a program that was the weakest at NCI, the Division of Cancer Control. It was actually called The Division of Resources Centers and Community Activities

(DRCCA). Many of the staff there had been the weakest staff in other divisions. They had been transferred into DRCCA by a committee that Bob Hoover [Robert N. Hoover, M.D.] and others were on. "Cancer control" was a term that Congress imposed on NCI in 1973, believing that NCI would not do cancer control unless they were required by Congress to do it. In other words, Congress wanted to see public benefit from NCI and not just discovery. Through the 1970s, the problem was that the NCI staff, with Diane Fink [Diane Fink, M.D.] and others as cancer control leaders, had defined cancer control as "not being research." They believed that under the NCI cancer control legislation you could not do research on how you would apply knowledge. The way they decided what would be funded as cancer control was this: They would sit around a table and decide that X would be a good thing, and so they would put money into it. It was not evidence based, but rather unsubstantiated opinions. That was foreign to me and other scientists. All aspects of research--basic discovery, clinical trials, and research on public health applications--are part of science. And I wanted to do research that led directly to public benefit. To be successful, I needed to change the whole climate, the whole staff, and I didn't feel I could do that under Dr. Upton, even though I liked him as a kind and sensitive person. But I felt that with Vince DeVita's backing, I would be able forcefully to change the nature of cancer control.

**VH:** There was a broader issue within NIH in that period, too, if I recall correctly. There was argument over the value of funding basic science versus targeted research, and there was considerable push-pull as to where the money ought to go. This issue at NCI may have been bigger because NCI had more money.

**PG:** Yes. Congress provided a line item for cancer control to assure that we would apply the knowledge gained through research. But through the '70s and into the early '80s, the definition of cancer control was very fuzzy. Cancer research leaders who wanted cancer control money would say, "Cancer control is rehabilitation; cancer control is something else, spend the money on what I want," and cancer control as a field wasn't going anywhere. It didn't have a clear mission. I felt a big missing link was that there was almost no cancer prevention. I saw many studies of epidemiological associations and rodent carcinogenesis, which were important, but the emphasis was on discovering relationships; there was no human intervention—a critical element for the work to be prevention. Etiology, to me, was knowing; prevention was doing, doing with a scientific basis in a way that would reduce the occurrence of cancer, and that's what I wanted to build.

**VH:** Before we get into the details of what you were doing, I want to discuss one side issue here. When you were setting up this division, they named you as Editor in Chief of the *Journal of the National Cancer Institute*, and you served from 1981 to 1987. Did you seek this responsibility, or was it assigned to you? And would you explain to me how you managed to edit a major journal, and set up and run a new division at the same time?

**PG:** Vince DeVita mentioned to me that the job was open. I said I'd love to be editor. I felt several things. Number one, as an editor of a journal, you're forced to look at areas of research that you otherwise might not pay attention to, and that that helped in getting a

broad vision and being integrative in the way you thought about things. I felt that was part of our role as leaders, as members of the Executive Committee of the National Cancer Institute, so I wanted to become editor because I thought it would pull me away from my strong focus to a broader focus that would be of benefit. Of course, it meant longer work hours, but there was very good staff, very good associate editors. John Bailar [John C. Bailar III, M.D., Ph.D.] had been editor before me, and, for those times, he had installed a good computer system that facilitated the management of the journal. I had some associates, such as Betsy Weisburger [Elizabeth K. Weisburger, Ph.D.], who were dedicated to working on it hard, so I could manage the journal. Being editor also brought a level of prestige to our division because people who wanted their research published knew that "Oh, well, you know, Greenwald as editor of *JNCI* must be an important person, so I'm going to pay attention to him."

**VH:** Thank you. Now, back to cancer prevention and control, your first task when you got here was to lead a re-thinking of organizational aims and processes and structure. Would you tell me about the process and how you did it?

**PG:** First of all, I did it with our Board of Scientific Counselors. In other words, I involved them. Lester Breslow [Lester Breslow, M.D.] was the chair. He was an internationally respected public health leader and we were very much in agreement about what was needed. I actually decided myself what we would do. Number one, I defined phases of cancer control. I defined cancer control as a science. I wrote a few papers about it, and defined five steps, phases of cancer control, and said, "We're going to step one, and when

we reach a point where we have enough evidence, we go to step two (by shifting funds) to step three, and it was all moving toward applications for public benefit.

I was fortunate enough to recruit as a deputy Joe Cullen [Joseph W. Cullen, Ph.D.], who had been at NCI before, but at this point, was at UCLA [University of California, Los Angeles]. Joe very interested in tobacco control, very outgoing, and very rigorous in his thinking. He was trained, actually, as a Jesuit brother in what's now the Culinary Institute of America – it was previously a Jesuit seminary near Hyde Park, New York. So he had Jesuit training in systematic thinking, and he applied my phases of cancer control to tobacco control. Joe and I looked at what was known about tobacco and at the NCI research portfolio on tobacco in 1982. It was all on the etiology of lung cancer. There was nothing on the etiology of smoking, how you prevent smoking, what you do about the problem--no research on that. There was redundant, ridiculously redundant research showing that smoking causes lung cancer, with little variations on that, but almost nothing on smoking prevention or cessation.

So we decide that first, we were going to do studies of preventing smoking in youth, of smoking cessation in individuals and in groups. That was phase one. When we felt we had enough of that, we said "We're not going to fund that anymore. If you want to do that, apply for a grant in the RO1 pool. We're going to fund community studies." How do you put it together? How do you affect groups? How do you affect women who smoke, blue collar workers who smoke, minorities who smoke? How do you get school systems to have smoking prevention programs? We did that for a while and got a body of evidence. Then we said, "Okay, we've got a lot there. We're going to move on now." We did a community trial where we randomized 22 communities, paired similar

demographics, and we applied what we knew in those. What could we do? That was called COMMIT [Community Intervention Trial for Smoking Cessation]. And then when that was done, we said "Okay, let's go for a broader theme. We're going to do what was called the ASSIST Program [Americans Stop Smoking Intervention Study], where we funded state health agencies together with those in the private sector--the American Cancer Society and others. We targeted a population of 95 million people, if you count the population of those states. We applied everything we knew and did that across the country.

There was also a part of this that we never told anyone about, but Joe and I would talk about it, and that was that we were funding people to do applied research. They were in the universities and public health departments, but we knew that the people we funded were the activists who were raising hell and promoting anti-smoking legislation and policies that we could not do as a government agency. Those people were the ones who actually moved society. They got smoke-free environments, they changed Clean Air Acts. For example, if you're in a public building and it had five changes of air an hour, if you allowed smoking, you would need more air exchanges per hour because you had to have lower particulate levels, and that would raise heating costs and air conditioning bills. So non-smoking policies for indoor air were implemented. We would support policies that we knew would force a change in smoking behavior across populations, and that could have a major impact. Joe Cullen later left to head a cancer center in Colorado.

**VH:** What time period are we talking about?

**PG:** We're talking about from about 1982-83 up into the early 90s. There was one other thing we did. You know that Dr. Koop, Chick Koop, or C. Everett Koop, [M.D.] lived next door to Harriet and me and for the eight years he was Surgeon General for the U.S. Public Health Service. He was a leader in tobacco control. He had come into the Federal government under Reagan [President Ronald Reagan]. At first, he was not liked by most people at NIH because he'd done a movie of rubber babies in the ocean, an anti-abortion film. But then his honesty and integrity came through in dealing with tobacco and with AIDS. He became a national hero. The Reagan group wanted to get rid of him but couldn't because he was so widely respected. Koop only had a staff of five, I believe, and he did not have the capability of doing the background research for his talks about tobacco. He just didn't have the staff. So what Joe Cullen, mainly, and I did was to help Koop with his tobacco work. I said, "Joe, don't tell me the details, but use our support contracts, and get all his background work done." We would spend about \$300,000 a year getting background information, so Koop, with his wonderful public ability, would talk about tobacco control, and he became the preeminent national and international leader in that effort.

**VH:** So you paid for Dr. Koop's tobacco control efforts, and Tony Fauci [Anthony S. Fauci, M.D.] paid for his AIDS efforts.

**PG:** We helped. We provided the backup so that he could do what he was terrific at. He needed staff work, and he didn't have it within the Public Health Service.

**VH:** In the 1983 paper that you mentioned earlier, "Cancer Control Research Directions and Opportunities," you laid out several premises. First was that the scientific method applied to cancer control, as much as to other research areas. The second was that the pursuit of excellence in science has primacy over other considerations. And the final premise was that we must build on our strengths across the spectrum from etiology to treatment. At this point in time, these premises seem obvious, but they must not have been when you arrived. Can you tell me how difficult it was to convince people of their truth?

**PG:** They were not only not obvious, they were in a sense denied. By that I mean that cancer control--the block of money in the NCI budget (\$30 million at first)--was defined as money that couldn't be used for research. To me, it should've been defined as money that could be used for what we now call translational research, for making the bridge from discovery to public benefit, whether it is patient benefit or public health benefit. Also, that cancer control itself is a subject of research, applied research. It needs the same criteria of evidence and rigorous thinking and careful interpretation and scientific debate that you need in every other area of science.

**VH:** Did you get much push back at NCI?

**PG:** I got support. Vince DeVita was great. He said, "Go to it." He supported whatever we wanted to do. I would explain it. He'd agree. We'd go ahead. And so the push back actually came more in the administrative area. I walked into a situation where I had a

staff of about 100. I was not satisfied with the overall quality of the staff, except for a small number of excellent people. What I did was to call people in individually and say, "Explain to me what you're doing, why, what you expect to accomplish over the next year. I'm going to hold you accountable for that." As a result, we went from 100 down to about 40. That was very tough, getting people to resign or move in the Federal Government, but afterwards, we built up to about 200. And the same situations arose as we shifted our budgets around. One example: We had a behavioral medicine program, which I terminated. I support behavioral research, but I terminated that program. The reason was that the main focus of the program was giving money to university psychology departments to support little psychology projects with their students. I didn't see how that would help progress against cancer. I wanted behavioral science, but I wanted it to improve behavior of institutions, behavior of policy makers, as well as behavior of individuals, but things that really counted. We supported studies into the eating behavior, tobacco control, focused where we knew there was a mission related orientation to it.

**VH:** It seems to me that you're defining cancer prevention as a subset of cancer control. In other words, cancer control includes more than cancer prevention includes.

**PG:** Right. That is the way the budget came. I wanted to focus primarily on prevention. My heart was in prevention. But there were parts of the budget that went beyond prevention in the program that I thought were important. I'll give you a couple of examples. We started in 1983 a community clinical oncology program. Actually, Vince and some of the

community oncologists were eager to have this. This is basically a network of physicians, nurses and their health support staffs across the country that were seeing patients. What Vince wanted and what the treatment people needed was more patients going into clinical trials. Our community oncology program provided that. So we set up a whole network that greatly increased the number of patients entering NCI-sponsored clinical trials. And over time, we proved that the quality of the participation was at least as good as at our major cancer centers, sometimes better, which cancer research physicians had been skeptical about.

But I had a secondary motive. And that was that I thought--I couldn't prove it absolutely, but I thought--that when doctors all across the country took part in trials, they saw them as their own trials. As the results came in, they believed the results, because they were their trials. You were a leg up in the diffusion and adoption of new medical knowledge that was a way of continuing medical education that would help patients all over the country. We pretty much showed that this was true for the doctors taking part. I had hoped it would diffuse into the hospitals and other doctors in the community. I'm not really sure how well it worked beyond the doctors in the program. We had an additional component that had to do with research on symptom management built into the community clinical oncology program. That was an important aspect of cancer control, but not cancer prevention.

**VH:** You noted in that same article that Bell Laboratories served as a model program to you for channeling successful basic research into effective applications. And at NIH, people felt very strongly about basic research, which we've said. You had to recruit people for

your new efforts. I want to list some names of those you hired and ask you to comment on them and what they did for you: Jerome Yates, Joe Cullen, who you've already mentioned, and Ed Sondik.

**PG:** Okay, they were all different. Joe Cullen was a behavioral scientist. A very talented, outgoing person who organized the national community against tobacco, and did a very effective job. Jerry Yates [Jerome W. Yates, MD], was a clinical doctor. He'd been at Roswell Park [Roswell Park Cancer Institute, Buffalo, NY]. He was an excellent, very honest clinical doctor, and savvy about clinical trials and building up the Community Clinical Oncology Program (CCOP). Later, Leslie Ford took over doing that. Jerry went on to be head of research for the American Cancer Society and later moved back to Buffalo.

I see two broad directions in prevention. The one that everyone understood was recommendations relating to public health and lifestyle. Don't smoke, eat a healthful diet, get some exercise, that kind of thing. The newer one is a medical direction.

Michael Sporn [Michael B. Sporn, M.D.] was the one who first came to me about this. He had created a lab of "chemoprevention" (he had coined this term) in 1976 at NCI, and when I arrived, in October 1981, Michael Sporn came to me and said, "Look at my data. What are you going to do about it?" People think of the field of epidemiology as science for public health, but none of the epidemiologists, except maybe Bill Blot [William J. Blot, Ph.D.], none of them came to me and said, "Look at our data. What are you going to do?" Most just wanted to publish papers about etiology, which would get them tenure

and promotions. Applying the findings was somebody else's problem. But Michael Sporn said, "Look, there's something useful in this." So we built a medical approach to chemoprevention of cancer. The rough comparison that is easy to understand is heart disease prevention. Find the risk, high blood pressure, high cholesterol. Bring it down with drugs, or with exercise and weight control. Our aim in medical prevention was to identify high risk and bring down the risk with drugs or lifestyle changes.

With Ed Sondik [Edward J. Sondik, Ph.D.], we were lucky in that Ed had been at the Heart Institute [National Heart, Lung, and Blood Institute (NHLBI)] before joining my division. Ed was an expert in systems--systems analysis operations research, and statistics. He has a very integrative mind about how things fit together, how you can move them forward, how one thing relates to another. Wonderful personality. He was, for a short time after that, acting director of NCI after Sam Broder [Samuel Broder, M.D., NCI director 1988-95] left. I thought Ed was the best NCI acting director we've had. Of course, he was just acting, and now he's the head of the National Center for Health Statistics. But he came to my division first to run the program that included Community Oncology. Then he became my deputy director. It was Ed and I who mainly led in developing NCI's goals for the year 2000 that we published in 1985. We had four committees related to our Board of Scientific Counselors work on the goals: one on prevention, one on early detection, one on treatment, and one on surveillance. These groups of experts looked at the most that could be accomplished if we applied everything we knew today, today being 1985. They thought it through very carefully, and we wrote out projections. For example, with respect to tobacco, if we could bring smoking rates down by 1990, here's the outcome. If we couldn't do it until 2000, here's the outcome.

Ed Sondik did a lot of the projection modeling and figuring out trend estimates. We felt early detection could only reduce deaths by 3 percent. And we ended up with a bottom line that we would be able to reduce cancer deaths by 25 to 50 percent, depending on how fast things were applied if, as a country, we fully applied our knowledge. We wrote a whole volume on this, in a 1986 issue of *NCI Monographs*.

To this day, all of it was generally accurate with one exception in the treatment area. Vince DeVita, with a few others, were very sold on a study that, I think, came from Montreal about prostate cancer treatment. It suggested that knocking out all the androgens would knock down the prostate cancer death rate tremendously, but it was wishful thinking in view of the much more limited benefit later seen with this therapy. The projection of decline in mortality through improved treatment turned out to be more than what could actually be accomplished. We ended up saying, "The historical rate of decline of improved therapy up until 1985 was about 1 percent a year. If we went to 1 1/2 percent, here's what we could get through new drug development and other therapeutics."

We made all these estimates, and we put it out there, big goals. Then we ran into the problem of needing to apply it. We got ridiculed. People said, "You set these goals and you haven't done anything." The problem with this was something that you mentioned. What does NIH see as its mission? My view was we never tried to reach the goals. We laid out the goals, but it required an aggressive national effort to achieve the goals, to implement them. Nobody wanted to implement. Nobody wanted to put NIH money into that. The money was never allocated. I came from a public health background. I'd been in New York State for 12 years, in the health department,

primarily. I knew that you could implement things like that, but the effort at NIH was almost completely focused on basic research and to some extent, clinical trials, but not public health applications of the research.

**VH:** I'd like to come back to your stop-smoking and tobacco control program. I have always wondered why it took so long for tobacco to be understood as addictive and for some chemical, like that in the patches and the chewing gum, to be available to help people quit smoking. Did your division have any kind of involvement in making that happen?

**PG:** To some extent. We focused on preventing the onset of smoking by children or delaying it, and to some extent on cessation. If you can keep children away from smoking beyond high school--up to age 20 or so--most wouldn't start at all. So that was a goal, to prevent smoking by school children. But as a cancer prevention program, that would take decades to have an impact because children wouldn't reach the cancer-risk age group for a long, long time. So we thought you also needed a smoking cessation program to have an impact early enough that we would see it. And yet, we knew that it took many years after a smoker stopped for the risk to come down significantly. Risk seemed to level off at the level where it was when a smoker stopped. Risk wouldn't get worse, but it took fifteen years or so to decline. In fact, today there are slightly more lung cancers occurring in people who are former smokers than current smokers because the former smokers are older and lung cancer takes a long time to develop. We did not test smoking prevention drugs, although some of that is done by other NIH institutes. There was an effort at behavioral approaches and at what kind of messages to get out.

One conclusion of tobacco control experts is that it's important for a doctor to ask a patient if he or she wants to quit. Ninety percent want to quit. The doctor needs to give the person a strong message that he/she should quit. A follow-up appointment should be set for the patient to come in and tell you how he/she is doing. Your nurse or someone else on the staff should call up the patient a few times and say, "How's it going?" These were things that might take you from a 15 percent to a 20 or 25 percent sustained cessation, where patients would quit for a year or more, but it was far from perfect.

**VH:** Were you all addressing the issue of why it wasn't doing any better?

**PG:** A little. One problem was competing against the billions of dollars in marketing tobacco. More recently, there is a drug called varenicline or Chantix by Pfizer that inhibits nicotine from reaching the receptors in the brain, and there are several vaccines that are in clinical trials now that do a similar thing. These may help people to stop smoking. But at that point in the 1980s, there was a little work from Ernst Wynder's group, but most was aimed at understanding the mechanisms of how tobacco harms you and behavioral approaches to prevention and cessation.

**VH:** I don't want to spend too much time on this, but there is also the argument that was going on whether or not smoking was an addiction.

**PG:** Whether we call it habituation or addiction, people get hooked.

**VH:** Let's move from smoking to chemoprevention. You said that you had been contacted by Michael Sporn about this. Now I think the public would love to think that they could take a pill that would prevent cancer, but that isn't chemoprevention. Would you define chemoprevention broadly and explain how it works and what you all did?

**PG:** Yes. I see chemoprevention as utilizing medical approaches to lowering your risk for cancer. Obviously, it's not total prevention, but it's the same as what heart disease people mean when they say prevention. It improves your chances of staying healthy; it lessens your risk. Initially, Michael Sporn, working with retinoids and Lee Wattenburg [Lee W. Wattenburg, M.D.] at the University of Minnesota, working with cruciferous vegetables--Brussels-sprout type vegetables, and the chemicals in them. Sporn and Wattenburg had evidence in animal models (mice) that you could prevent some cancers--quite a few--with chemoprevention. They were saying that we should look at this clinically. At NCI, I built the first clinical program. It included preclinical development and testing to early phase human clinical research. We looked at the array of potential chemicals that might have benefits and figured out how to move them forward. Some were drugs and some were food compounds, vitamins, minerals, other bioactive food compounds.

We started a process that would lead us into the trials. We set aside monies and issued requests for applications to get a community of scientists working on those trials, mainly aiming toward early (phase II) studies. At the same time about 1983, we started two very large trials. One was in Linxian, China. Actually, the idea came from NCI epidemiologists, Bill Blot [William J. Blot, Ph.D.], and Phil Taylor [Philip R. Taylor, M.D.]. They thought about it before I came on the scene. We jumped in and worked on

a large vitamin and mineral study of what we thought, initially, was cancer of the esophagus. Linxian, China was the place that had the highest rate of esophageal cancer in the world. It turned out to be cancer of both the esophagus and the upper part of the stomach. We ended up showing that a combination of selenium, vitamin E and beta carotene cut the stomach cancer rate by about a fifth. One thing I wanted to do was get a big trial rolling before other results came in, so that even if the first results were negative, people wouldn't say, "Oh, there's nothing to that field." I wanted to be sure the field would take hold.

At the same time, we thought that beta carotene, which was being promoted as having health benefits by the vitamin pill industry, could be preventive against lung cancer, and that vitamin E had some possibilities of being preventive in reducing the risk of lung cancer in smokers. So we got together with Finnish scientists, excellent scientists. One of them, Olli Heinonen [O.P. Heinonen, M.D.] had been a classmate of mine at Harvard School of Public Health and was a leader of public health in Finland. We designed a trial in 29,000 heavy smokers that could be done very efficiently through what were old TB clinics around Finland. We did an intervention trial that we thought might prevent some lung cancer. Years later, there was a very interesting outcome, which was not what we expected. That was that beta carotene made things worse for smokers. Also, we found that vitamin E seemed to reduce prostate cancer by a third. That was not an initial study hypothesis. So there were two interesting outcomes.

One thing about the beta carotene: There's misinterpretation of it today. At that point in time, a lot of epidemiologists were implying that beta carotene prevented cancer.

The vitamin pill industry had picked that up and taught the public the words “beta carotene,” like it was this magical vitamin pill or food constituent. The industry was selling it with very flimsy evidence. So I think the epidemiologists ended up misleading us because they'd see a marker of maybe vegetable intake. But in the trial, if I round off the numbers, you will see what we found. There were 29,000 people in the trial divided into half. So about 14,500 got beta carotene and 14,500 got placebo for beta carotene. Of the group on beta carotene, roughly six men--they were all men--per thousand per year developed lung cancer. Of those on placebo, about five per thousand per year developed lung cancer, a difference of one per thousand per year--which is a 20 percent increase. Actually, the increase was a 16 percent higher rate of lung cancer for the men who got beta carotene. In my view, the most astute physician, or the best epidemiologist, could never pick up that tiny difference in practice (one per thousand per year). It took a very well-designed, top-of-the-line, randomized clinical trial to show this. This has great public health importance, and it was the first study that suggested, "Hold on, now. Taking large doses of one vitamin or another doesn't necessarily mean you're going to be better off. You might be harmed" You need evidence before you go promoting high dosage supplement use.

**VH:** I was trying to remember when the dietary supplements program got started. It was designed so there would be no FDA [Food and Drug Administration] regulation. But there would continue to be an impetus from the commercial side to convince the public that dietary supplements were good things.

**PG:** Right. And because of the way the Food and Drug Administration legislation is written, the FDA does not have authority to insist on efficacy before the marketing of products for supplements, vitamins and minerals. They don't have the authority, and there were people in Congress from states that had supplement industries and who insisted on that kind of legislation.

**VH:** This brings us back to the need to communicate to the public why you need to run a clinical trial, because there is a great deal of public trust that if “they” put it out there on the TV, it's bound to be true.

**PG:** Right. It's a distortion. The same thing is happening with antioxidants. The public has been taught the word “antioxidants.” To me, there is probably no such thing. They're all redox systems. The same chemical can be anti-oxidant in one microenvironment, and pro-oxidant in another. With beta carotene maybe in the aerated lung where you have tobacco carcinogens, the beta carotene was pro-oxidant. You have to really understand the chemistry. You don't want to oversimplify and then hype something where there's little evidence.

**VH:** Indeed. In your 1996 article in *Scientific American* about chemoprevention, it suggested to me that the surface has really just been scratched in this area. Can you tell me where it stands now?

**PG:** Yes, I think the surface still has just been scratched. I say that because we have a lot of leads--many, many. It's almost the opposite problem of cancer treatment. In treatment, the problem is finding drugs that are very effective. There are only a few drugs a year coming out of an enormous effort. What we have in prevention is that a lot of drugs or bioactive food compounds that look like they potentially could have benefits. We don't have the resources to follow through and test them all in clinical research. We have very few clinical trials in cancer prevention. They're all expensive, and they take many years. Some of them are \$100 million trials. To me, that's not expensive because if you look at the aggregate investment, it's small compared to other fields. But if you look at each individual trial, what we have are people saying, "Oh, my gosh, look how many labs you could fund for that money." They almost want us to prove the efficacy of a prevention effort before we do the trial, and that's impossible. So I think our investment is small, and the potential in the field is enormous. We're also looking at how best to get buy-in by industry, how to get buy-in at NCI and NIH. That varies according to who is the director of NCI. The current director does not like large trials. He prefers NCI to invest in basic sciences, early discovery. This limits our getting new large clinical trials in place. It's always been uphill, but it was a lot easier under Vince DeVita, a lot easier with Sam Broder, both of whom understood the need for a strong clinical trials program. But starting with Klausner [Richard D. Klausner, M.D., NCI director 1995-2001], it's been a bit of a problem.

**VH:** Let's talk about the diet and cancer branch which was established in 1983. I'd like to know who headed this effort and that it started out with your knowing that diet and eating

behaviors are thought to be related to approximately one-third of all cancers. Tell me about this program.

**PG:** Okay. Although many of us thought about this earlier, in 1981, two eminent British epidemiologists, Richard Doll and Richard Peto, under a contract from NCI, looked at avoidable causes of cancer and published *The Causes of Cancer: Quantitative Estimates of Avoidable Risks of Cancer in the United States Today*. That's where the estimate of roughly a third--within broad boundaries of uncertainty--but roughly a third of all cancer has dietary determinants. The last time I saw Doll, which was ten or twelve years ago, before he died, he put the bounds at 40 to 60 percent of cancer related to diet (and I would say eating behavior and exercise). That came largely from looking at international differences, at effects of migration. When people move from one country to another, they – or especially their children – take on the risk of the place to which they move. The most logical explanation of this is change in lifestyle, with diet as the biggest factor. So we had this rough estimate of about a third. We have some general epidemiologic data, not a lot of basic nutritional science, some debates in the nutrition community over dietary fat and other factors. The first thing we wanted to do was to get some sound research going. Two people who did this in my division were Dr. Ritva Butrum [Ritva Butrum, Ph.D.] and Carolyn Clifford [Carolyn K. Clifford, Ph.D.]. Ritva was very dynamic in coming forward with requests for applications and set asides, where we put money aside just to get people doing research on diet and cancer. That built up the program. Then we became involved with some public issues. One was fiber, and the other was fat. I'll take one at a time.

In February 1984, I went to the Food and Drug Administration. Sanford Miller, Sandy Miller [Sanford A. Miller, Ph.D.], was head of the food side of the FDA, and Frank Young [Frank E. Young, M.D.] was head of the FDA. I went there because I thought they should change their “standards of identity.” Their “standards of identity” defined a food, and I didn't think these standards promoted healthful diets. So, for example, if you had a margarine, you had to use words like “artificial” to describe it. For a food that might be more healthful, you had to use words that had a negative connotation because of industry lobbying for butter or dairy or whatever. So I went to them and said, “Why don't you change your standards to be on the side of good health?” And Sandy Miller said, “Well, we appreciate your thinking. We've been doing things this way for 75 years. We're not going to change. Do it your own way. Good luck.”

Later that year there was a lot of discussion about fiber. A physician named Dennis Burkitt [Dennis P. Burkitt, M.D.], of Burkitt's lymphoma, had published articles about the size of the stool of Africans, and the fact that they had very few colon diseases—cancer, appendicitis, GI problems. Burkitt attributed that to more fiber in their diet. When he visited Washington, D.C., he convinced Vince DeVita that his theory was correct. DeVita went on the McNeil Lehrer show [“The McNeil Lehrer News Hour,” PBS] and said, “I eat a bran muffin every day.”

Up to that point, I'd been talking about the need to eat vegetables, fruits and whole grains. Elaine Lanza [Elaine Lanza, Ph.D.] and I did a review of the evidence, and I said, “Okay, we can say fiber.” With Paul Van Nevel of the NCI Office of Communication, NCI started a cancer prevention awareness campaign later that year, in 1984. Margaret Heckler, who was DHHS [Department of Health and Human Services] Secretary under

Ronald Reagan [President Ronald Reagan, 1981-89], wanted to kick it off. She was a pleasant lady. She came to Masur Auditorium [at NIH] and announced the cancer prevention campaign and said that we would invite industry in to take part. The next day or within a couple of days, someone from Kellogg's [Kellogg Company] called and said, "We'd like to hear what you're saying." So we said, "Sure." They showed up with scientists--good academic, nutritional scientists and others from Kellogg. Paul and I spent an afternoon with them going through our evidence and discussing our message, "Eat a variety of foods high in fiber." They said, "We're going to put it on our cereal box." So we said, "Okay, but you have to put the whole message. You can't just say 'eat more fiber'." They agreed to that. And, literally, they did that. But I think they probably had focus groups, because the impression that came across from the cereal boxes was that "fiber" meant All-Bran, their cereal product. That's the impression that the public got. Kellogg marketed this, and they blocked out all the TV stations several times with their ads, and over the next three years, high-fiber cereal sales went up dramatically, although the sales tapered off a few years later. The FDA was furious at me because up until that point, no health claims were allowed on foods. The Reagan Administration used this program as a lever to reduce regulation so that implied health claims on foods were more or less allowed, and that put the FDA on the spot, and they blamed me.

But fiber consumption went up. A little later, about 1987, I wanted state health agencies to use their databases to promote public health and cancer prevention, so we set money aside for that. A group in California came in with what they were calling the Five A Day program. Basically, it encouraged people to eat five to nine vegetables and fruits every day. We looked at that and decided we loved the public, very positive

message, and we revamped it with them. California held the license, and we started the Five A Day program with a partnership of government, industry, and the private sector. In industry, this was mainly the produce manufacturers and the large supermarket chains. But the industry people said, "Oh, you're too slow, government. We'll set up our own corporation and call it the 'Five A Day' for better health foundation." They collected \$400,000 in a day or so to get things started. We set up collaboration where NCI would have to approve the messages. They would not be allowed to market something with the Five A Day label that also had a down side. For example, they couldn't sell French fries under this label. They could sell a baked potato. They could sell broccoli, but not broccoli and cheese because of the high fat content of cheese even though it is a good food.

Within less than a year, there were billions of gross impressions with the Five A Day label. An example of a gross impression is one person seeing a stamp on a plastic bag in the market one time, or seeing one ad in a magazine. And 80 percent of the supermarkets in the country were using this message. It was all over the country. From our evaluation, I think it improved the understanding, although it's still hard to get kids to eat their vegetables.

**VH:** One related question. Did your division have any input to the development of the food pyramid publicized by the U.S. Department of Agriculture (USDA)?

**PG:** Not the recent one. In fact, I don't like it. No food is shown on the current pyramid display. You can't tell what you should be eating. Also, individual variability may be a

fact, but you look at the current pyramid and you don't know what you're supposed to do. We've had mixed relations with the USDA, some of it outstanding with Beltsville scientists who are interested in health. They have some good labs, and we collaborate. We still have people who work with them. And there's a political overlay at the leadership of USDA. This varies with the politics of the administration, so it's a little tricky; but, in general, it's been okay.

The situation with dietary fat was a different story. I came to NCI in 1981. I had been on a committee of the Institute of Medicine, the Food and Nutrition Board, which I joined when I was in New York State. I was invited to join because I had helped them with a committee on nitrites--nitrites and nitrates--and I'd written a part of the report. The Institute of Medicine asked me to be on the Food and Nutrition Board, which is a big deal to food people, but I didn't even know what it was when I joined. Well, I got there and found bickering between leading nutrition scientists over the fat message. They were accusing each other of misrepresenting the evidence. It was terrible because the older members of the group were accusing the newer people. The older group was saying, "You don't have the evidence on fat," and the newer group was saying, "Fat increases your cancer risk." I looked at it and said, "There is evidence that fat increases your risk," so they started accusing me of being a plant from NCI, even though I'd been on the Food and Nutrition Board before I came to NCI.

The root of the problem was in the way fat was measured. The standard way in epidemiology was to use a food frequency questionnaire, which measures the percent of your diet that is fat. It's a way of adjusting for energy. It's not grams of fat, which is the total amount of fat that are counted, but just the percent of fat in the overall diet. Even

though we were promoting guidelines saying “cut down fat,” meaning cut the percent of calories from fat, we would joke on the side that you could actually implement the guidelines by drinking more Coke--that is, if you took in more calories, but they were sugar calories, non-fat calories, the total calories would go up and your percent of calories from fat would go down. In that sense, the guidelines were absurd. It would have been better to focus on grams. What never occurred to us when we were saying to cut fat was that industry would come in over the next five to ten years with many, many foods that they marketed as low fat. These were useless calorie junk foods. And people got fat. They were eating all this stuff, portion sizes were going up, volume was sold as a value, whether it was fast food or major restaurants, plate sizes were getting bigger and bigger. Kids could go into a movie house and have a 32- or 40-ounce Coke, which was nothing but sugar water and caffeine. So we had this growing problem of obesity, a sedentary society plus calories and calories. I think a lot of it happened because we didn't look at the fat issue exactly right.

Then all through the 1980s, starting maybe '83 or '84, my colleagues Maureen Henderson [Maureen Henderson, M.D.], who was an epidemiologist at that point in Seattle at the University of Washington, and Ross Prentice [Ross Prentice, Ph.D.] , who's one of the best statisticians in the world and was head of the group at University of Washington, and I wanted to do a woman's health trial, a randomized clinical trial to determine if you cut calories from fat, would you lower breast cancer risk? We would bring this proposal to the National Cancer Advisory Board (NCAB) time after time after time, and the NCAB would come in loaded to shoot us down. Before I could get out a second sentence, they'd be attacking this idea because they were counting up how many

labs you would fund for the \$100 million we wanted to do this trial. That went on until Bernadine Healy [Bernadine Healy, M.D., NIH director 1991-93] became director of the National Institutes of Health.

When Sam Broder was director of NCI, Bernadine Healy came in as director of NIH. Her background was cardiology, and she knew that the idea that almost every woman at or after menopause should take estrogens had never been proven in a clinical trial. It was promoted from about 1960 or '61, to women, especially California women, that you were not normal if you didn't take estrogen. But it had never been proven, and Healy wanted to do the clinical trial to find out. So she outlined at a meeting of the institute-center-division (ICD) directors at NIH that she wanted a "woman's health initiative" (the term Maureen, Ross, and I had used was "women's health trial"). Sam Broder came back from the ICD meeting and said to the executive committee at NCI, "Peter, Bernadine Healy wants to do a women's health initiative. Here's your chance." My interpretation of this was, "Here's your chance to get NIH rather than NCI to pay for your trial."

I got together with Ed Sondik, my deputy, who's an outstanding scientist who knows how to design trials. And we asked Bill Harlan [William R. Harlan, M.D.], who was at the Heart Institute [NHLBI], running their clinical trials program, to participate with us, because we knew we needed to write a proposal that would include more than just NCI. Sam told me about the possibility on Wednesday. By the time I got Ed and Bill on board, it was already Thursday. Our aim was to get a proposal in Bernadine Healy's lap by that Friday, because we knew that each Friday evening, she'd fly back home to Cleveland where her husband was a top surgeon at the Cleveland Clinic. We

thought that if she had the proposal, she could read it on the airplane. So in 24 hours, we wrote a proposal to do a woman's health initiative that included the dietary fat study; the calcium and bone loss prevention study; and the estrogen-progestin study. We thought this would give Healy a starting point for discussion. We did a back-of-the-envelope quick calculation and came up with a \$500 million price tag because we knew what trials cost.

The next Monday, she walked into Congress and announced that NIH would do a woman's health initiative, and that it would cost \$500 million. It was a spectacular example of leadership in medicine. She was wonderful. Some people at NIH hated it and didn't care for her doing this, but I was really proud of her. And nobody could say no after that. It was announced to Congress. We were doing it. Then there was about a year of committees and discussions, mostly led by Jacques Rossouw [Jacques E. Rossouw, M.D.] and others at the Heart Institute, because Healy wanted them to be in the lead, and that was fine. That kicked off the women's health initiative. Bernadine Healy was the leader.

After the year of discussions, the project ended up very much like what we originally wrote, but there was input from many experts from all across the country. I think a lot of the intellectual input and clinical trial expertise came from the heart disease people at NHLBI, Jacques Rossouw, particularly. A number of NIH staff, especially women scientists, took part.

There were interesting outcomes, some of them a surprise. The study about effects of taking estrogen plus progestin after menopause showed that this drug regimen probably did harm. This outcome probably stopped much of the use of hormone

replacement therapy. After that the breast cancer rate across the country started to drop after women stopped taking estrogen plus progestin pills. The study of the relationship of dietary fat to breast cancer in the Women's Health Initiative, to me, was inconclusive. The data indicate no significant statistical association, but when you look at the trend over time, you see no change between the intervention and control groups for about four years. And then those on low fat start to do slightly better—they have a lower incidence of breast cancer--and the improvement increases toward the time when the trial is stopped. When you look at the trend line, you think, "That's a study that needs a longer follow-up." It might be that there was a benefit early in carcinogenesis, but you need to wait longer before you can see the effect.

**VH:** How do these studies compare with the Framingham Heart Study? Do we need that kind of long term study to understand if dietary fat does have a causative effect on breast cancer?

**PG:** We need a study of years longer than the Women's Health Initiative. A longer follow-up study is underway. I can give you another example from this trial. Let's take the hormone part and use an imaginary example. Let's say that there's an effect on cognitive function of estrogen use, and the time to event is many years longer than the time-to-event for heart attacks. Say it's twenty years later, you either have a benefit or harm to your brain. You won't know that if you don't do a very long-term follow-up. And there's no bio-marker study or other quick way of shortening that time line. Once you make this enormous investment to do the trial at all, the investment for continued follow up after

the intervention has stopped is fairly small but very important. There are always people who say, "Why do you have to go any further? Let's stop the study." But in my view, you want the long-term follow-up. You get a lot out of it, and sometimes in these add-on studies that were not part of the main plan, but which look at the person as a whole in other disease categories have valuable findings.

**VH:** In some respects, it's just like finance: it is difficult to convince people that a big investment now will pay off over time when people only want to know what they will get in a short period of time.

**PG:** Right. Also, with preventive interventions, I worry about adverse events that occur late. In cancer therapy, especially for late stage cancer, you don't want bad side effects, but you're willing to take the risk to pretty large extent. In prevention, you don't want that risk; you want to absolutely minimize adverse events. Prevention and treatment are coming close together with adjuvant therapy, that is, treatment of early-stage disease. So, for example, with localized breast cancer, when many women now have a lumpectomy and radiation, you have to treat many to have a clear benefit for some. When the survival is very good, to show an additional benefit, you need a large population and a long-term study, and you don't want much toxicity. So the challenge is not so different between therapy of early cancers where treatment is very effective and prevention.

**VH:** In 1983, you created the Community Clinical Oncology Program, or CCOP [pronounced C-COP]. And in 1996, you had 51 programs in 30 states, funded by the CCOP, and there

are now at least 214 hospitals involved. Tell me about how this is helping the expansion of prevention, as well as therapy.

**PG:** Part of our aim was to increase the number of patients on trials. We now contribute to about a third of all patients on cancer treatment trials that are run by the Federal Government. So CCOP contributes a huge proportion. But my division does not drive what drugs are being tested. That's our Division of Cancer Treatment and Diagnosis. Several of our large cancer prevention trials have been run through the CCOP, the Community Clinical Oncology Program. I can describe the breast cancer prevention trials, then the prostate cancer trials, then those for colorectal cancer prevention.

On breast cancer, NCI supports a national clinical trials group called NSABP, National Surgical Adjuvant Breast and Bowel Project--there are two B's in the formal name, but there's only one in the initials. It was created and led from many years by Bernard Fisher [Bernard Fisher, M.D.], an outstanding surgeon at the University of Pittsburgh, who set up this national network. The NSABP was one of the biggest contributors to progress against breast cancer in the whole past century. They led almost every major study in treatment and in prevention. There may have been others who did similar studies, but Fisher's group were huge world leaders. One study they did utilized Tamoxifen for adjuvant therapy of breast cancer. That is, a woman who had early stage breast cancer would be treated with Tamoxifen to lower the chance of recurrence; what was observed was that there were about half as many new cancers in the opposite breast in addition to lower recurrence of the primary cancer. That observation and the basic science behind our thinking informed the first breast cancer prevention trial.

We sponsored the trial in over 13,000 women. It was run as a cooperative agreement with the NSABP, who ran the trial. Healthy women who did not have cancer but had the risk of a 60-year old (even though they may have been younger) were randomized to take Tamoxifen or a placebo. This trial showed a 49-percent reduction in the occurrence of new breast cancer in the Tamoxifen group as compared to the control group; so we prevented about half of breast cancer using this estrogen receptor modulator called Tamoxifen. There were a few side effects, a little more endometrial cancer, though none fatal, and as with every estrogenic compound, more blood clot problems, some of which were serious. On balance, most women were better off taking Tamoxifen. The NSABP and we had proved definitively for the first time that a medical approach can prevent some breast cancer.

**VH:** How is this going to interface with the rise of individualized genetics? I mean, will you be able to say this woman will benefit from Tamoxifen but that one may not?

**PG:** That's hard to answer because there are not enough women who have the BRCA-1 or BRCA-2 genes or other, not yet proven, genes that raise breast cancer risk for us to say whether these women benefit or not. There are little hints that they might to some extent, but we don't have the answer from this study. NIH promises "personalized medicine," but we are not there yet. I think of it as "stratified medicine." That is, you can stratify into risk groups. For example, there is a group of breast cancer patients with the HER2 gene amplified. About 20 percent of breast cancer patients have this amplified gene that has a bad outcome. You can aim for treating those with a particular therapy. So there

may be groups that we can address. You're not going to treat each individual as a special case, but if you're in those groups, you might get a different therapy or prevention than someone else. We may be able to do innovative studies using biorepositories, the bloods that were collected and the white cells in large clinical trials, to identify people with various risks and targets for new drug development.

The follow-through on the breast cancer studies, however, is interesting. The next thing that happened while the Tamoxifen study was going on was a study of a drug called Raloxifene. Raloxifene was being used for osteoporosis, to prevent progression of osteoporosis and to prevent fractures. There was a study called MORE, Multiple Outcomes of Raloxifene Efficacy, that showed that women on Raloxifene not only had improvement and fewer fractures, they also had less breast cancer, 60 or 65 percent less, something around there. Women with osteoporosis aren't particularly at high risk for breast cancer. If anything, their estrogens are a little low. But we now had two drugs that seemed to have benefits in preventing breast cancer. We decided we needed a head-to-head comparison, to try to see which one works better for whom. So we started another trial, again with NSABP in the lead, called the STAR trial, Study of Tamoxifen and Raloxifene, in over 19,000 women. The outcome was that the two drugs were equivalent in reducing breast cancer occurrence. When you looked at the adverse events and the overall picture, in general, the Raloxifene looked a little better, and the company then got Raloxifene approved by the Food and Drug Administration for reducing breast cancer risk in post-menopausal women. This past Mother's Day, the drug company started an advertising campaign. This showed the women with a towel around them saying, "If you want to prevent breast cancer and osteoporosis, raise your hand."

**VH:** Yes, I've seen the ad and tried to figure out what it meant.

**PG:** It's an odd ad. They're marketing the drug for osteoporosis in women at risk for breast cancer, and it helps against both. So that was fine.

The next problem I ran into was with the current NCI director, if this is not jumping ahead too much. We had these two drugs that prevent about half of breast cancer. What they actually prevent is the hormonally-driven breast cancers, which is about 70 percent of breast cancer, called ER-positive, or estrogen-receptor positive breast cancer. They don't prevent the 30 percent that are ER-negative. We were developing a group of studies to see if we can address the ER-negative. But we couldn't get the funds to stimulate clinical trials aimed at preventing ER-negative breast cancer. Back to the ER-positive, there's another set of compounds called aromatase inhibitors that prevent you from making estrogen, and we thought might be more effective in preventing the ER-positive breast cancers. Potentially, testing aromatase inhibitors could show us how to prevent as much as 70 percent of post-menopausal breast cancer. So the NASBP group and my colleagues and I in the NCI Division of Cancer Prevention wanted to do a trial, the head-to-head comparison of Raloxifene, the best selective estrogen receptor modulator versus an aromatase inhibitor. These two drugs might differ in the extent of benefits, and in their adverse event profile, and you need a balanced picture before deciding what is best for each woman who is interested in preventing breast cancer in this way.

The NASBP put in their application for this trial. They got the best review, the best score [from the NIH peer review group] they ever got in their whole history. Many well-informed breast cancer experts wanted this trial. The current NCI director [John E. Niederhuber, M.D., appointed NCI director 2006] blocked it without giving a logical reason. He wanted to give priority to basic research. He didn't like the study, never explained why. Even though I think he had already made up his mind, he said that he wanted to hear discussion at the National Cancer Advisory Board about this. He set up a committee to look at it. The committee was stacked toward those who did not want to invest in this trial. There was a discussion at the National Cancer Advisory Board. I spoke out clearly, defended the trial, and he has retaliated ever since.

He retaliated by lowering my personnel report rating. We have something called the COER, the Commissioned Officer Effectiveness Report. It's your personnel report if you're in the U.S. Public Health Service. Niederhuber turned to Al Rabson [Alan S. Rabson, M.D.], his deputy, who is well liked, but who at this point is a pathetic old man who just wants to hang onto his job. So Al Rabson wrote me up as mediocre compared to other officers. He told me on the phone that it was because Dr. Niederhuber was still "mad at me" for speaking out and giving my scientific opinion that we wanted to do a trial that might demonstrate that we can prevent up to 70 percent of post-menopausal breast cancer. The COER may not really matter, because those who get it know me. The NCI director didn't want to do the trial because he wanted to put the money in his own pet projects. That fight about resource allocation is still going on.

**VH:** Which illustrates clearly that scientific priorities are not things easily agreed upon.

**PG:** Right. But you have a problem when you have a director whose management style is very centralized, top down; he's the expert on everything. And that's who we have now.

**VH:** In December 1983, when you were setting up the new Division of Cancer Prevention and Control, you wanted to base its activities on scientific data. And the first thing that I saw that you did was to develop something called a Prevention Trials Decision Network, the PTDN, as a means to formalize the prioritization and evaluation process. There was also the End Points and Biomarkers Committee. Would you talk about those two and what was going on here?

**PG:** We wanted to build criteria of evidence and logic that would fit cancer prevention. So we defined some of these things. We started to work with them. Some of it was very practical, and some sort of faded away. We used the Prevention Trials Decision Network for a while, but there weren't enough different trials to need a formal structure. We ended up going case by case, gathering people who were expert in the various fields, and arguing each trial as we went along. There was one committee set up. I'm not sure what the name of it was. It was chaired by Barry Kramer [Barry Kramer, M.D.], and co-chaired by Bernard Levin (it's spelled L-E-V-I-N, but he pronounces it Levine) [Bernard Levin, M.D.], who was head of prevention at M.D. Anderson Cancer Center. They co-chaired a committee of our Board of Scientific Counselors that came up with a plan for an Early Detection Research Network. The basic issue was that a lot of people were working on biomarkers without a really rigorous definition what a biomarker was. Was it

something associated with a cancer? Was it something on the etiologic pathway? Was it something that provided a prognosis about outcome of therapy? Was it something that told you risk or exposure, (for example, dietary exposure)? So the concept of a biomarker was fuzzy and broad, but many people were talking about doing biomarker research, and they all had their own definitions of biomarker. There were a myriad of markers. A major problem was that the number that were validated, meaning clinically useful and proven, was zero

The closest thing to a proven biomarker is what pathologists call a pre-cancerous lesion, such as an adenomatous polyp or leukoplakia of the mouth (the general term for this is intraepithelial neoplasia). Another example of a proven marker is late-stage pap test before cancer develops. Molecular markers can be useful but have not been proven as definitive measures for cancer detection or as end-point measures of efficacy of a drug. The Levin-Kramer committee recommended that we set up an Early Detection Research Network that would do developmental work and validation on biomarkers. A great deal of biomarker discovery was already going on, so partly we were trying to catalyze validation, moving this forward into clinically useful tests. The NCI program is managed by Sudhin Srirastava [Sudhin Srirastava, Ph.D.].

I'll give you one example. David Sidransky [David Sidransky, M.D.], a world-class scientist at Johns Hopkins, had done a study of mitochondrial DNA mutations that he felt might predict risk of head and neck cancer and bladder cancer. In his research, he utilized a rigorous sequencing of DNA that most labs cannot do. So we went to NIST, the National Institute of Standards and Technology, and said, "Can you make this into some sort of chip that any good pathology lab can use so that we can see if others can

replicate this test and see if it holds up in larger clinical studies?" We had to take it from the beautiful discovery work of a first class scientist and see if the technique could be developed into something that could be replicated and used by others and eventually brought into clinical testing. This work is still going on, sponsored by NCI's Early Detection Research Network. There are other examples of that sort of effort with a number of different biomarkers that we are trying to move toward clinical usefulness.

What we have found is that biomarker validation is a costly and long-term process. It's not easy. There is much wishful thinking about biomarkers, but to really work them out so they're useful and proven is not so easy, and it takes time. Our Early Detection Research Network is set up to do that, and it's a unique, highly respected national program.

**VH:** Another one of the overarching programs that I see in this period is the SEER program, Surveillance Epidemiology and End Results. Would you talk a little more about it?

**PG:** SEER is the cancer registry system that was already established before I joined NCI. Brenda Edwards [Brenda K. Edwards, Ph.D.], who is a meticulous statistician and excellent manager of science, was heading this program when I came in 1981, and she still is the leader. SEER provides the data for U.S. cancer statistics. I didn't have to do much except support what Brenda and her staff already were doing, except to help them to expand SEER. We wanted to make sure that we covered enough of the major population subgroups so there would be enough Hispanics, enough African Americans, Asian Americans, and native Americans. Also, we wanted to do special studies where

the registry was used to identify patients in defined geographic areas—studies that would give specific information about health outcomes. There is a field of research called Outcomes Research.

The cancer registry program was expanded with CDC [Centers for Disease Control and Prevention] supporting some non-SEER state registries. A lot of states--most of them--now have some sort of cancer registry system. I had a rule of thumb that you should spend at least as much on use of the data as you do on collecting the data and publishing annual reports. SEER did that in the sense that all of NCI was using it, especially the epidemiologists. But in many places, the means have become the ends; a state may have a registry, but they just collect data and don't use it very effectively.

**VH:** Along with expanding SEER, you created a special population studies branch and a minority-based program too.

**PG:** Initially, about 1983 or so, Lou Sullivan [Louis W. Sullivan, M.D.] was a member of my Board of Scientific Counselors. He was president of Morehouse [Morehouse School of Medicine] in Atlanta, Georgia. A very skilled public health physician, Claudia Baquet [Claudia R. Baquet, M.D.], was running our minority program. Claudia and Lou made a strong case that we needed an African American initiative. They called it the National Black Leadership Initiative on Cancer. They developed it. I watched and supported them, but they were the leaders, Lou Sullivan and Claudia Baquet. They got the historically black medical schools and some other groups into science, the science of applications of knowledge, and built a strong network across the country. After that, in

1989, Lou Sullivan was named DHHS Secretary. He still called back every week when he was DHHS Secretary to talk to Claudia, and so we had an ongoing connection. They were outstanding, and they kept moving this program forward. It worked well. Claudia is now at University of Maryland.

This was our chief method of addressing disparities. We aimed to attract minority scientists who would be leaders in cancer control and not just fund one-shot deals that would end when the money ran out. We wanted something more permanent. Drs. Baquet and Sullivan were very savvy. We used the National Black Leadership Initiative on Cancer as a model to build the Hispanic Leadership Initiative on Cancer, and an Appalachia Initiative. These helped to address disparity issues.

**VH:** And speaking to disparity issues, you made a very interesting statement that I noted: "Research is underway that will help standardize the way in which health care providers assess health quality of life for minority populations." Why is assessing health quality of life for minority populations different from assessing the health quality of life for the majority population?

**PG:** I don't think it's different in what you want to accomplish. There are cultural differences in perception and understanding, such as whether going to a hospital is a benefit or a place to die. There are differences in access to care, and there still are prejudices. These are diminishing, but we still see prejudices about how people are perceived and what kind of therapy they'll get according to who they are. And although it's been changing over time, there were issues over cultural sensitivity, understanding, and access.

**VH:** Are the different programs, for example, for trying to reach one minority teenage population with stop smoking messages from another?

**PG:** I don't always think of it so much now as minority groups, but rather as the lower income, poorly educated. We now have now a large middle class of minority families, and they're the same as the white middle class in terms of health messages that reach them. Harold Freeman [Harold P. Freeman, M.D.] is a person who speaks a lot about that. He chaired the President's Cancer Panel [1991-2004] and worked with us. I think you have to look at who the group is that you really want to help impact. If you stratify the education level, it's the poor minorities plus poor whites who still suffer in health care.

**VH:** What about the differences within an ethnic group?

**PG:** Again, I'm not an expert, but for example, I think the mainly Puerto Rican Americans in Florida are different from the New York City Hispanics, are different from the Mexican Americans. So even within a group like Hispanics, there's a lot of variety. And if you take Native Americans, there are huge differences between some of the tribal areas. The same is true of African Americans—we have tremendous heterogeneity. In terms of genetics, when you look at the scientific details, these old ways of classifying population groups don't make much sense.

**VH:** What implications does this have for cancer prevention efforts?

**PG:** It's hard to generalize, but we want to aim for a common goal. A physician named Al Haynes [M. Alfred Haynes, M.D.] once served on our Board of Scientific Counselors. I asked him to chair the Board. He was the president of the Drew Medical School [Charles Drew University of Medicine and Science] in Los Angeles. I didn't realize it when I asked him, but I was told later that he was the first African American ever to chair an NCI advisory group. The point he kept stressing was, "We have the same goals as everyone else. We want to reach the same reduction of cancer rates, and we don't want a different goal that's less rigorous, but is going to cost more to reach it. You need more people working on this. You have to understand, cancer control in minority populations is intensive. You have to spend a lot of face time with people talking with them." So it's a matter of how much investment it takes, how much thinking, how much community participation to really reach the same goal? It takes a lot more effort and costs a lot more, but it is important.

**VH:** In the mid 1980s, from '83 to '87, and then in the early 1990s, you served on the U.S. National Committee for the International Union Against Cancer [IUCC]. Would you tell me about this group and what your role was?

**PG:** I didn't have a big role. IUCC is loosely tied to the American Cancer Society. It's a very large international group. They mainly try to apply information of cancer control and bring together people in different countries. It helps us to address global problems in cancer control. Usually some of the more advanced western countries are together, and

the others are trying to learn from them. We tend to get involved by giving talks at international meetings and in training.

There was one initiative, it wasn't with UICC but with the World Health Organization (WHO). I don't remember who was head of WHO at that time, but WHO had almost no tobacco control in its entire program. With Dr. Koop in the lead, we worked out that we, NCI, would pay for two staff to work in Geneva with the World Health Organization for two years, and then WHO would pick up the cost of building a tobacco control program. We did our part, and after the two years, they reneged. They didn't do it until they got a new WHO leader from Norway, Gro Brundtland [Gro Harlem Brundtland, M.D., WHO Director-General, 1998-2003]. She built a strong tobacco control program. But before that, they had almost nothing.

**VH:** In 1986, Vince DeVita resigned as NCI director and was replaced by Samuel Broder. Would you take just a minute and describe Dr. Broder's leadership style, his goals for the NCI, and how cancer prevention fit into those goals?

**PG:** Sam Broder was very bright. I liked him a lot. I still consider him a friend. He had developed AZT [the antiretroviral AIDS drug, azidothymidine], along with Burroughs Wellcome [Burroughs Wellcome pharmaceutical company] and did the early testing of AIDS treatment at the NIH Clinical Center. That gave him the reputation that led to his being named NCI director. Before that, his forte was clinical medicine, when he would troop around Building 10, the Clinical Center, with a lot of fellows, very bright, a good sense of humor, and well liked – I liked him on the NCI Executive Committee. We

would debate things. He had no problem debating. He had this kind of Talmudic logic, but if you disagreed with him, there was no problem; and you still respected each other when the debate was over.

Everything went well with his directorship, until he ran into one problem that I thought he mishandled badly. That was in the breast cancer prevention trial with Tamoxifen. There was a doctor in Montreal who abused the criteria for women to enter the trial. Essentially, a woman needed to have a mammogram after entering the trial for breast cancer prevention, but this physician put on the trial women who had received their exam before the date, which was not allowed in the protocol for the trial. This was discovered by the group in Pittsburgh and reported to NIH, but nothing was done about it for six months. Then John Dingell, the Congressman from Michigan, decided to make a big investigation, and Sam had trouble standing up to his authority and prosecutorial style. He could not handle this aggressive congressman attacking him, so what he did was pass the blame onto Bernie Fisher. That was unfair and caused a big mess.

I would stand up for Bernie Fisher and say, "Sam, why don't you go to Congress and just say we had a problem, we took care of it, we're moving forward," and Sam would be furious with me. He'd say, "If you don't like the way NCI's being run, you can resign today, or you can go to the President and ask him to get my resignation." This happened about five times. Sam would be very excited and just go off the wall with it. He didn't carry a grudge afterwards, but that's what he said. Eventually, Bernie Fisher sued and won, and what I just said to you is in the legal transcript from when the lawyers interviewed me. Bernie knew it. I would talk to him during this period, as would Leslie Ford [Leslie Ford, M.D.], my associate director for clinical research and herself a leader

in breast cancer research. We would say, "You know, all of us at NCI are not your enemies, Bernie." It was very hard, especially on Bernie Fisher's wife and on his head statistician, Carol Redman [Carol K. Redman, Ph.D.], who just could not take it. She left Pittsburgh because of that. It put unfair pressure on one of the greatest men in the history of breast cancer research. That was terrible. If it wasn't for that, I would've said Sam Broder was a wonderful NCI director. In a way, I miss him because his style was good compared to some of the later directors. I see him occasionally now and he likes to say, "Now don't you miss me? You never thought you'd miss me, did you?"

**VH:** In 1989, you created the Applied Research Branch to focus on three areas of research: Health Services and Economics, Modeling and Statistical Methods, and Cancer Risk Assessment. Tell me about this branch and who headed it.

**PG:** It first was headed by Ed Sondik. Also, Larry Kessler [Larry Kessler, Sc.D], who later went to the FDA. Martin Brown [Martin L. Brown, Ph.D.] was an economist looking at health services; these and others were key people in the program. They were interested in health outcomes, how you evaluate them, how you use population data, like from the SEER registry, in an analytical way, and they were world class. A lot of their work helped groups like Medicare in thinking about how to make policy. They would contribute useful information. This is a strong group. Rachel Ballard-Barbash [Rachel Ballard-Barbash, M.D.] was part of it and, eventually, led it. Then under Rick Klausner, it got broken off into another division that he established. That's another big issue.

**VH:** That issue we'll get to in the next interview.

**PG:** Yes.

**VH:** The Preventive Oncology Branch, 1991. Tell me about its work.

**PG:** This training program actually was begun way before that, I think 1983 or '84. I wanted to start a training program where we would bring people in and train them to build the field for the future. We had an educator, a doctor of education, named Robert Burnite with whom I worked. We set up a training program which provided a summer course, and then set up a mentorship for two years or so. We aimed to build a new generation of physicians and scientists for cancer prevention. Later, we formed the program into an Office of Preventive Oncology, aimed at training. It eventually included a summer program with dozens of international people, plus postdoctoral fellowship program where physicians or Ph.D. scientists could be mentored in different areas of prevention across NCI.

**VH:** One of the very important prevention trials you did through the Community Clinical Oncology Program related to prostate cancer. I'd like to hear more about this study, especially the fact that you became a subject in it.

**PG:** Okay. That was the Prostate Cancer Prevention Trial. There's a drug called finasteride or "Proscar" that had been developed and used to treat enlarged prostates, which cause

obstructive symptoms of urine output. The drug would shrink the gland and help improve urine flow. Testosterone is the main male hormone. In the prostate, it gets converted to a more potent hormone called dihydrotestosterone (DHT), and the finasteride inhibits the conversion of testosterone to the far more potent DHT. So we and Merck [Merck & Co. pharmaceutical company] felt that it might be useful in preventing prostate cancer. We wanted to set up a trial, which we did, with another cooperative clinical cancer research group called SWOG, the Southwest Oncology Group. The trial was aimed at seeing if we could prevent prostate cancer with this drug. Because African American men have the highest rate of prostate cancer in the world, when we set up the trial, we wanted to over-sample African American men. Earlier, when we had started the breast cancer prevention trial, we had a hardboiled hearing in Congress, when NIH director Bernadine Healy, my colleague Leslie Ford, and I had to defend why we were giving a drug that we knew would have some side effects to healthy women. We went to Congress and defended it. In the prostate trial now we were going to over-sample black men, and the legacy of the Tuskegee syphilis study in black men meant that there would likely be questions about the possibility of doing of harm.

We never start a trial unless there's something called equipoise, that is, we don't know the answer. If we knew the answer, we wouldn't do the trial. There's a balance between what you think will work and what you're not sure about. So we were setting up a trial to over-sample black men, and we pictured the worst-case scenario: "Supposing it comes out wrong? How are you going to explain that you over-sampled black men, did harm?" The women and younger members of my staff said, "No problem, Peter, you go on the trial. And if it comes out wrong, you can go to Congress and say, 'Look, I knew

the benefits and potential risks and I went on the trial myself, so there." So I was one of the 18,000 men who went on the trial. At the end of that seven years of intervention, no matter what your PSA [prostate-specific antigen screening test] was, you got a biopsy. I went through everything, including having my prostate biopsied, when my PSA was very low (favorable).

**VH:** Which wasn't very pleasant, I dare say.

**PG:** Well, true. But the biopsy was negative, so that was good.

**VH:** And what about the trial itself? What kind of results did you get?

**PG:** We showed that we could reduce the occurrence rate of prostate cancer by a quarter, a 25 percent reduction. We showed definitively we could prevent some prostate cancer. But there was a problem at the time of the first report of the study. While those on the drug finasteride had that 25 percent reduction, whether it was clinical disease developing during the seven years of intervention, or biopsy results at the end, the men on the finasteride who did develop cancer appeared to have slightly more aggressive cancers. There's a grading system for prostate cancer called Gleason grade, and it showed that those taking finasteride had more higher-grade tumors. That was a problem that we had to understand. As the Southwest Oncology Group scientists and we studied it over the past three years, it became clear that there is differential shrinkage of the gland by the drug, so that normal tissue shrinks by about a quarter, and the pre-cancerous and

cancerous tissue shrinks less or doesn't shrink at all. So you shrink the gland by a quarter, then you put needles in for a biopsy--six then, now urologists use ten or twelve eighteen-gauge needles. You're more likely to hit an aggressive-looking part of the gland because the normal part of the gland has shrunk. Just as a matter of anatomy, you'll hit more of the aggressive-looking part. So the explanation for this unusual situation was that it represented an artifact of diagnosis. Taking this into account, it was estimated that we actually prevented more like 30 percent of the cancers rather than 25 percent.

Now we have definitive proof that we can prevent at least a quarter of prostate cancer. We're expecting the Southwest Oncology Group and the company to bring this to the FDA for approval of finasteride for lowering the risk of prostate cancer, because we can't educate the public about it until we get FDA approval. That's where we are today. I'm pretty sure that's going to happen. And then we need an educational campaign.

**VH:** I'm going to stop today with one broad philosophical question for you. After the germ theory became so completely established in infectious diseases, the thinking of almost everybody was that there must be a single cause for everything, and of course they were looking for the single cause of cancer.

**PG:** Right.

**VH:** Are we back now to a situation where we need to think about multiple causation? When you say you can prevent 30 percent of a type of cancer, it sounds like there must be more than one thing that's leading to these cancers.

**PG:** It is many more than one. I think of necessary causes and sufficient causes. So necessary means if you don't have that cause, you won't get the cancer. For example, human papilloma virus is a necessary cause of cancer of the cervix. There may be other-- probably are other contributing factors. Number of sexual partners. Some people even say smoking. There are multiple things that affect the environment and may contribute to whether you develop cervical cancer, hygiene possibly. But if you don't have the human papilloma virus, you won't get cervical cancer, so you can prevent it by vaccinating against the virus. You have to vaccinate early enough in life before a woman is exposed.

But now you take the diet-related cancers. They are not like tobacco where you smoke or you don't smoke. Everyone's eating, and it's the relative amounts of calories and nutrients that may promote or inhibit cancer development. The relative amount probably can affect the microenvironment that allows the tumor to develop, grow or not grow. It's a very complex issue. I don't think it's likely we'll have a single cause for some cancers. We will for some; not for others. There are going to be some that are just part of your normal response to DNA damage. For example, if a cancer results from everyday exposure to cosmic rays, you can't really prevent it. We're going to have to learn how to deal with that. Detect it early, treat it effectively. Prevention is a partial answer, a very important one, I think the most important one. Prevention is under-supported, but it's not going to be a complete answer, and there's not one cause.

**VH:** With that, I'm going to stop for today, and thank you very much.