DIVISION OF CANCER PREVENTION

ORAL HISTORY PROJECT

THIRD INTERVIEW WITH

Dr. Peter Greenwald

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National Cancer Institute
Division of Cancer Prevention Oral History Project
Interview with Peter Greenwald
Conducted on December 12, 2008, by Victoria Harden

VH: This is the third in a series of interviews with Dr. Peter Greenwald, Director of the Division of Cancer Prevention, National Cancer Institute, about the history of his division. We are again talking in Dr. Greenwald's office at the National Institutes of Health. It is December 12, 2008, and the interviewer is Victoria Harden.

Dr. Greenwald, we left off in the mid nineties when we stopped, and I would like to start with the shift in leadership in 1995 when Dr. Broder [Samuel Broder, M.D., Director, NCI, 1988-1995] resigned at NCI director and was replaced by Richard Klausner [Richard D. Klausner, M.D., Director, NCI, 1995-2001]. Would you comment on Dr. Klausner's priorities as director and what impact they had on your program?

PG: Yes. First of all, let me just say there was a short interim period when Ed Sondik [Edward J. Sondik, Ph.D.] directed the National Cancer Institute as Acting Director. He was one of the best people we ever had. He has a wonderful perspective and balance. He knows operations research and statistics, so I liked that period when Ed led the NCI.

Rick Klausner came in as a very bright basic scientist, knowing a bit about clinical research but more focused on basic science. He was very smart, but conniving, as we found out over time. There was a problem that I never really understood, but he didn't relate to me from the beginning. I suspected some ulterior motives that didn't directly have to do with me, but I can't document whether or not that is true. My guess is that Barbara Rimer [Barbara K. Rimer, Dr.PH], who was a behavioral scientist in Health

Communications, was chairing the National Cancer Advisory Board (NCAB), a major advisory board to the NCI, and Rick, wanted someone more like a National Academy of Sciences member to chair the NCAB. He really wanted Mike Bishop [J. Michael Bishop, M.D.], a Nobel prize winner, who was Chancellor of the University of California, San Francisco, Medical Center and Cancer Center. Mike's a wonderful person, very well balanced. Everyone likes him, including me, and respects him. So during the summer, while I was away in Banff, Canada, Rick announced he's dividing the Division of Cancer Prevention Control into two parts.

VH: Did he give a reason?

PG: I never got a concrete explanation. It was, I guess, to build up what he called the Division of DCCPS, Division of Cancer Control and Population Sciences, in which he put nearly all the behavioral focus activities, including tobacco, diet, and communications research. He also put epidemiology and surveillance in DCCPS; that is, the extramural grants management part of epidemiology, not the intramural part. He convinced Barbara Rimer to head that division, which took her out of the position as chair of the National Cancer Advisory Board and allowed Rick to appoint Mike Bishop to chair of the NCAB. So the division that I had been running was cut in half. Again, I can't document his motivations. He never explained it, but I suspected that he didn't care that much about cancer control or cancer prevention, and this kind of manipulation allowed him to achieve his other objectives.

VH: I'd like to sidetrack you one minute here and just ask—this is a broader question that has come up several times. Is the reason many people within the cancer community don't like cancer prevention because it doesn't have the same scientific cachet of winning a Nobel prize, or are there other reasons to de-emphasize prevention and emphasize something else?

PG: I don't think it has to do primarily with the glory of it, which is limited for all clinical research, including prevention and public health research. I think it is a combination. One, if you look at the establishment of cancer centers, their largely non-NCI funding stream comes from taking care of patients, being at the forefront of getting new therapies, and where their NCI grant support mainly is for basic research. Prevention has always been fuzzed up with basic and epidemiological studies of etiology, with causation. These are related but are not exactly the same. Prevention means doing something. Etiology means knowing something. We did not have a lot of knowledge to build upon for prevention, especially in the early eighties. It's a changing picture now. We have had some successes that people understand, and you see a shift in attitudes, but it took over twenty years to get here.

People go where they think they can succeed, and availability of research funds is a major driving factor. It's an issue that has to do with the rewards system. How do scientists get tenure and promotions? University incentives fit into what their departments want and where they know they can get grants easily. Unfortunately, I think you get them easily when you're doing studies where already a lot is known, because your applications don't have as many issues that can be attacked by the reviewers. So,

for example, if you put an application in nutritional science, which is a very complex area, it can be very difficult because there are always areas that you can't really specify clearly. If I would pick one factor, I would say mainly the rewards system for the scientists and for the physicians drives the direction of science. What influences how doctors see their role as physicians does not include getting reimbursed for prevention.

VH: I remember that you were made to reapply for your job under Klausner. But after they did a national search, they discovered you were already the best person for the job.

PG: Well, it was a surprise. Klausner set up a committee to evaluate the Division of Cancer Prevention—i.e., me—headed by Ed Bresnick [Edward Bresnick, M.D.]. I interviewed every member of the committee after their report was written. It was prepared without the participation of many of the committee members and aimed only to find the negatives. I thought the report was going to be used as a lever to not select me. But then there was a later committee that selected from the applicants for division director, of which I was one. That committee had very good people on it who knew the field. They essentially told Klausner I was the only highly qualified applicant. There was one person way below me, and all the others were not qualified. So Klausner then selected me, to the dismay of Bresnick, who had chaired this committee and who has since died. But Klausner went along with it. I mean, it wasn't a huge issue for him, I don't think.

VH: It wasn't personal animosity towards you, then.

PG: I couldn't be sure. I think he just had his own priorities. One thing he respected was knowledge and the ability to debate, and that was a strong suit for me. He was fine with that, and we moved our programs forward. Once he got what he wanted, he was okay.

VH: In this new position as the Director of the Division of Cancer Prevention, it's my understanding you did not have an intramural program any longer, is that correct?

PG: That was another thing that Klausner did, and it wasn't directed at me personally. There was a report to the NCAB called Bishop-Calabresi, since Mike Bishop, the chair of the NCAB, chaired the committee who wrote it with Paul Calabresi [Paul Calabresi, M.D.], who was the head of oncology at Rhode Island Hospital. Their report essentially said that NCI should be like the rest of NIH, where there's a complete separation of intramural from extramural. It implied that there would be some conflict if the separation didn't exist. Rick Klausner implemented that recommendation at NCI. That meant that the few intramural programs that we had were taken away, but it also impacted other parts of NCI—for example, epidemiology was set up to separate intramural from extramural, and labs were all put in the Center for Cancer Research. We've swung back a bit since then, especially as today we get into more and more team science where you need people from different disciplines working together and where the intramural investigators have to work with extramural investigators for progress. So we're swinging back. That change was a change in science management systems; it was not directed at me.

VH: At this point, you apparently established a new organizational matrix structure at this time which gives explicit attention to prevention science foundation areas and targets organ research groups such as breast cancer, prostate, gastrointestinal, and lung. Tell me about this.

PG: We thought through a new structure with a fellow named Arnold Kaluzny [Arnold D. Kaluzny, Ph.D.]. He's an expert at the University of North Carolina on management and business systems as they apply to health. He led an evaluation of several of our programs and at one point chaired our Board of Scientific Counselors, so he knows a great deal about us. His expertise was in organization theory and practical applications of it. We thought we'd set up a matrix as a way of getting people to work together in appropriate team relationships, building up basic nutritional science, and keeping the translational research and clinical research focused and moving toward public benefit.

The basic structure was fine. The matrix part of it didn't work very well. The reason for that was the way the government at NCI is set up. I did not have the ability to put resources directly into the teams in the matrix. The resources went to the different research groups, more or less like branches, and so we'd set up teams and we'd track them, but we didn't allocate major resources to the teams. The matrix approach then fizzled. We ended up saying, "Here's what we need to get done. Let's get it done." The team matrix part of the structure was soft and didn't help us accomplish a lot. We still organize the division into foundations of cancer prevention and the clinical groups, and they're very, very strong. We have wonderful people leading them and they've made a lot of progress. If we need a team, we will set it up for that one purpose.

VH: You also added other functions, including a communications function and a protocol office.

PG: Yes. The protocol office helps us with quality control and tracking of clinical trials. We hold investigational new drug (IND) applications with the FDA [Food and Drug Administration]. Over time, we've had sixty-two of them. There are about a dozen or so active today.

VH: What is the role of the Division of Cancer Prevention in IND applications?

PG: The reason we are involved is that there is a lot of basic science related to the medical approaches to prevention. We're developing preventive drugs--we're also getting extramural scientists to do that. Some are bioactive food compounds that have low toxicity that might be useful in prevention. When outside investigators do this, unless they're at a large cancer center, they rarely have the capability to take their discoveries and bring them into clinical trials. We had to create a bridge. You need studies of toxicity, of safety, of efficacy. You need at least two animal models like a mouse and a dog. The kind of studies you need to do to get through the Food and Drug Administration are not the sort of things that you can get a grant to do. It's not original research. Therefore, we set up an IND capability to bridge from basic to clinical research, and to hold INDs for a number of studies being conducted by extramural scientists.

VH: I wonder if any of the other institutes have the resources to do this.

PG: Our Division of Cancer Treatment does this extensively.

VH: That's within NCI, though. I was wondering about other institutes.

PG: We've had people from the smaller institutes at NIH come to NCI and say, "We need this, but we can't do it." Or, "Show us how to do it." I'm sure NIAID [National Institute of Allergy and Infectious Diseases] and the Heart Institute [National Heart, Lung, and Blood Institute (NHLBI)] manage INDs, and maybe NIDDK [National Institute of Diabetes and Digestive and Kidney Diseases]. The others may not; they tend to be limited to a grants program and a small intramural program.

VH: So they don't have a bridge mechanism.

PG: No, some are very limited in their capacity to bridge into clinical trials. Sometimes they'll pay for piggyback studies on our trials—for example, a study of eye disease or a study of cognitive function. But they can't do it alone.

VH: I know that one of the reasons AZT was able to be identified as a therapy for AIDS was because NCI had in place the cancer drug screening program.

PG: Right. On AIDS, there were two basic capabilities that allowed NCI to make progress. One was, as you mentioned, that Sam Broder was trained in drug development. Burroughs Wellcome was investigating AZT; Sam did the early clinical testing at the NIH Clinical Center. The other one was retrovirus research in the 1970s, which led to the development of the technology of molecular biology, and that's what laid the groundwork for Bob Gallo [Robert C. Gallo, M.D.] to do his AIDS research, aiming at uncovering the HIV agent along with Montagnier [Luc Montagnier, M.D.], and his other work, which assured the safety of the blood supply.

VH: It is very interesting to me how the great investment in cancer that was started in the seventies has begun to pay off. But we're getting away from your division. I was looking at the names of your project teams, and I would like to ask you to talk about some of them. "Molecular targets for dietary prevention of prostate cancer," for example. What were you looking for here?

PG: We have a combination of some hints from epidemiology that what you eat may affect either getting or, more likely, getting the aggressive prostate cancer. For example, some studies suggest that a high fat diet raises risk and lycopene (the red color in tomatoes) lowers risk. So there were associations, but we couldn't say that they represented cause and effect. We need to study that more.

Another even stronger thing we did related to some major clinical trials we had going. The Prostate Cancer Prevention Trial, which showed we could reduce prostate cancer by a quarter, provided probably the best biorepository in the world for studying

prostate cancer, because we had biopsy material carefully collected on the control group as well as those on the drug and bloods collected years before the diagnosis of prostate cancer. The material was well documented with epidemiological and clinical histories about the individuals. If someone wanted to study mechanisms of the development of prostate cancer or the benefits and limitations of PSA [prostate specific antigen] screening, we had the material. We wanted to open it up so that scientists anywhere, as long as they met certain criteria and did not interfere with the trial itself, would be able to do research using the material. We set up the biorepositories and the data systems to allow research to move forward in a way that never would be possible without the trials.

VH: This program was for people who were getting grants? They could utilize this information?

PG: Yes. They'd have to come to us first, and some of them didn't always realize that. They needed to get from us a letter saying, "We'll be happy to provide this to you under these conditions, and you can do your studies." They would have to include that letter in their grant applications to show that they had the feasibility of doing their studies.

VH: What about the HPV [human papilloma virus] vaccine against cervical cancer?

PG: That landmark research was done by Doug Lowy [Douglas R. Lowy, M.D.] and John Schiller [John T. Schiller, Ph.D.] in NCI's intramural research program. They figured out how to make virus-like-particles which would provide immunity against specific types of

the human papillomavirus accounting for about 70% of cancer of the cervix. This is the vaccine. Unfortunately, the vaccine is expensive. In our chemoprevention agent development, we are working with a group in India to see if we can develop a much cheaper vaccine that uses subunits from the capsule of HPV. We think that in most countries where cervical cancer is rampant, they can't afford the vaccines that are being developed now. Maybe the price will come down, but we thought some alternatives that could be made really cheaply would help. So we have a track related to developing an alternative vaccine.

VH: That's still ongoing?

PG: That's still ongoing. We also have the pathologist who developed the Bethesda System for reading Pap tests, Diane Solomon [Diane Solomon, M.D.]. She is world-class. She has been involved in the HPV trials with Schiller [John T. Schiller, Ph.D.] and Lowy [Douglas R. Lowy, M.D.]. And with Mark Schiffman [Mark Schiffman, M.D.], the epidemiologist leading these studies. Diane lends her expertise as a pathologist expert in cancer of the cervix.

VH: What about the Ovarian Cancer Prevention Initiative?

PG: Ovarian cancer is tougher. We're not very far along in ovarian cancer. There is research using a chicken egg model and analysis of risk related to BRCA [breast cancer] genes. We are supporting studies of methods of early detection because it's hard to detect

ovarian cancer early. So far they haven't paid off. These are tests of different protein patterns in the blood. They are worth pursuing, but we don't have an answer yet.

VH: But you don't have any chemoprevention or dietary links or anything like that that are promising?

PG: We know that birth control pills can cut the risk of ovarian cancer in half, if you take them for a number of years. This has been known for quite a while. There aren't other strong new leads. There's more work on biomarker development.

VH: Would you explain biomarkers once again? That's something that I think is very difficult for people to understand.

PG: Yes, and even the scientists confuse what we mean by "biomarkers" because there's not clarity of definition. To me, there are a whole range of biomarker types. A marker can be a blood test or a urine test or a saliva test or pathology test on tissue. One type of marker tells you about susceptibility (e.g., a genetic marker) and another about risk.

VH: Like the cholesterol test for heart disease? If your cholesterol number is over a specific value, you are at greater risk for heart disease.

PG: Exactly. But that test tells you not only about susceptibility, but also where you are on the pathway toward causation of heart disease. The LDL/HDL [low-density

lipoprotein/high-density lipoprotein] proportion part of the test can tell you that. Then, after you prove that a certain marker is indicative of the pathway to causation, you may be on the way toward proving that if you change your cholesterol, you change your heart disease risk. The final proof requires a clinical trial. More recent heart studies look at changing the lipid profile without going all the way to looking at change rates of heart attacks, even though some cardiologists still want proof of an impact on heart attacks and deaths. We're not that far along in cancer, but we do try to identify markers of susceptibility. It might be your genes, like BRCA-1 and BRCA-2 that are associated with elevated breast cancer rates. These are all markers of susceptibility. Epidemiological factors associated with high risk usually are not considered biomarkers—e.g., have you had prior biopsies, has your mother or sister had breast cancer, how old were you at your first pregnancy and first full-term childbirth?

Carcinogenesis is a long process. We actually think the disease is not cancer; it's carcinogenesis. This is just like in heart disease, where the actual disease is atherosclerosis. It's not fractures that is the disease; it's osteoporosis. It can be decades, even more than one decade for a disease to develop to the point of cancer, heart attack, or fractures. We're trying to find ways to identify carcinogenesis earlier, then to do something to change the trajectory so you don't get clinical cancer. Our whole Early Detection Research Network is aimed at finding out and validating markers to help us do this.

Now, the big problem is that you have to validate those biomarkers, and doing that is just as complex as drug development, if not more. You first have to demonstrate that you have a test that's potentially useful. Can it be replicated by other scientists? Can

you do it efficiently enough at a low enough cost and in a large enough group of people that you can then study it clinically? Once you study it clinically, if we give you some blind specimens that we may have from one of our trials, like the Prostate, Lung, Colon, and Ovary trial of early detection for over 150,000 people, can you predict clinical cancer from the bloods drawn several years before the diagnosis? If you can do that, should we do a clinical trial where we randomize people based on the new early detection test to see if we can reduce mortality compared to a control group? Do we have an intervention that lessens risk? Does the test make a difference? Because if you can't do anything about intervening in the disease process, what's the point?

So it is a long, long process. We have set up a major national program—with several international collaborators—aimed at discovering and validating biomarkers. The first validation step is: Can another lab replicate your test? If the test is developed in a complex high-tech system, can you simplify it enough so that others can use it—that is, can you make a simple test out of it? Besides helping to develop new early detection tests, this program saves money by rejecting early tests that cannot be validated or have no practical value.

VH: Is it ever going to be as simple as the cholesterol test? If I have a blood test and my cholesterol is at a certain number, they tell me, "You need to get it down to another particular number." What I'm asking really is whether one test will work for all types of carcinogenesis. It seems that different types of cancer are so complex that you won't ever be able to have just one marker for all cancers. How about one marker for each type of cancer?

PG: That might be feasible. The definition of a "type" of cancer is changing. There are lots of types that have the same histology, but when you start looking at the molecular level at pathways of genes, it looks almost like every person has a different kind of cancer. People tend to talk about developing "personalized medicine," but that's only starting to take hold. Nobody's going to make a drug for one person. I think we are moving towards "stratified medicine." We may be able to group people according to certain measures, probably molecular blood measures, and I think that we will eventually be able to detect pre-cancer or cancer early and have therapeutic options both for preventing progression to clinical cancer, if we detect pre-cancer, or treating any clinical cancer we find.

VH: As you spoke about groups, I thought about the recommendation that people over fifty have a colonoscopy, and if polyps are found, they should be taken out before they have time to become malignant.

PG: Right. We know that some polyps will advance to cancer, and we know that the more advanced polyps are more likely to become malignant. But if you take all polyps out and if you ask those patients who have polyps to be screened more often, you're more likely to prevent more colon cancer. We are now supporting studies of noninvasive methods of screening, such as testing for a panel of mutated DNAs in the stool. The idea is that such a test will be able to tell the probability of whether you have a polyp or have cancer without the invasive colonoscopy. Then, if it's likely that you have a problem, that is

when you have the colonoscopy. People don't want to get colonoscopies, so even though we know it will reduce colon cancer by 70 to 80 percent, if people won't go and have the test, it won't be an effective tool. We think we need a noninvasive test that people will be willing to take, and that's what we're aiming for.

VH: In 2001, you published an article in the *Journal of Toxicology* that reviewed the emphasis in cancer research from the 1970s to 2001. You noted the change from the seventies' emphasis on etiology, discovering a cause—environmental factors, possible viruses, genetics—and that this was also the period that sparked this interest in the relationship between diet and cancer and in chemoprevention things like vitamin C. You developed the Early Detection Research Network, and I wondered if you have some examples from this program as to what has been developed beyond work on biomarkers.

PG: Let me take nutrition. In nutrition we have strong trends suggesting that what you eat affects your chances of getting cancer, but the data are imprecise. We know that eating more vegetables and fruits, keeping your portion size down, and getting exercise is helpful. But the data came from epidemiology, which mainly shows you associations. On a mechanistic level we had only educated guesses or circumstantial evidence. We felt that we needed to build a much stronger basic nutritional science program, and we've been doing that. It's working, but it's quite uphill, because at NIH, the focus is mainly on drug development and not on nutrition. With basic nutritional science, you have all the complexities that you would have in drug research, even more. There is the individual variability of how people respond to diet, how they metabolize foods, what they absorb.

Then there are difference in the foods, and the foods are changing rapidly. What you eat today is different from what you ate twenty years ago. What's available in the supermarket is different. It's going to be different again in the future, and so we have to take that into account. Your diet over your lifespan may differ from recent diet. It's a moving target, but yet we need to do the basic nutritional science.

Then there was the hype that followed hints from research that some specific nutrients might be beneficial. Beta carotene was first. It was hyped and sold to the public implying a cancer preventive. It didn't work, but we had to do a trial to show that. Selenium and Vitamin E were hyped and sold as a preventive for prostate cancer. That didn't work, either, and it took a long-term, expensive trial to prove that.

We can also run early detection trials. In 1993, we started the Prostate, Lung, Colon, and Ovary (PLCO) screening trial. Over 75,000 men and 75,000 women take part in this trial. The aim is to see whether the currently available early detection tests will lower mortality from these four cancers. The trial still is going on, because it takes many years for the cancer to develop. Survival for prostate and colorectal cancers is long, which means a long wait for trials that have a mortality end point. The PLCO has a biorepository which is extremely valuable, because we have stored blood and DNA for up to six years before the time of diagnosis.

VH: When you say biorepository, do you mean tissue samples?

PG: In this case we have blood samples and DNA on most participants. We do have tissue for many of the people who develop cancer.

VH: Just to get it on the record, when you have a repository like this and you have clinical information about the people who participated in a study, those people's medical records are not individually available. They are protected, right?

PG: They are protected, but we often need and use information about individuals. A lot of attention is given to assuring that we have consent from the participants that covers the planned use of the specimens. And if we want to use the data for some other purpose that we didn't think about initially, we might have to "re-consent"—go through the informed consent process again--and that gets a little tricky because each of the places participating have their own institutional review boards (IRBs), and the IRBs might not all behave the same way, so we have to deal with each individually. If we want to do a follow-up, and the follow-up requires contacting people, we have to consider whether we have permission to do it. In some cases, yes, but in some others, no. There are always these kind of issues that take a lot of time and energy and care to protect the privacy and the rights of individuals.

VH: Would you tell me about the National Lung Screening Trial (NLST)?

PG: We know that CT [computed tomography] screening of the lungs in smokers can detect small lesions, including early lung cancers. We don't know if that does any good in reducing mortality or whether it may actually do harm. It could do harm because when you biopsy in someone with chronic bronchitis or other lung problems, you are doing an

invasive procedure. That can do quite a bit of harm. The NLST screens 53,000 people who have a smoking history to see whether CT screening, as compared to chest x-ray screening, will reduce the mortality from lung cancer.

VH: When will it be completed?

PG: I keep blinded to these things. We have an independent data safety monitoring board (DSMB) that sees unblinded data periodically and tells us (1) this is never going to show a benefit, so stop the trial; or (2) you're showing a clear benefit, so it is time to let people know about it; or (3) you should continue the trial because results so far are inconclusive.

VH: I see. So there's not necessarily a fixed period.

PG: Right. There are power calculations which take into account how long it will take to reach the endpoints that are part of the design, but flexibility comes from having an independent data safety monitoring board. The DSMB also adds this impartiality with uninvolved scientists and physicians looking at the data, making sure there's no safety issue that we didn't anticipate, and looking out for the participants of the trial as well as keeping the integrity and the rigor of design intact.

VH: In September 2001, Dr. Klausner stepped down as director, and he was succeeded by Andrew von Eschenbach [Andrew C. von Eschenbach, M.D., Director, NCI, 2001-2006].

Would you describe Dr. von Eschenbach's priorities and administrative style and how it affected your program in cancer prevention?

PG: I have a lot of respect for Dr. von Eschenbach, but he came in under the Bush [President George W. Bush] administration, which wasn't supportive of big government. Dr. von Eschenbach was very close to the administration, to Bush himself, and was a very outgoing, open-minded leader. He pretty much allowed things to proceed, encouraged people as they developed their research ideas, but there were never a lot of resources. We had gone through a period of increasing budgets just before Dr. von Eschenbach came in. And it was not because of him but because of the way funds were allocated to NIH and NCI that the budget peaked and then started a downturn in real dollars. This made it very hard to start new initiatives. The problem was, we were in a changing budgetary climate, which affected all of NIH, including NCI.

VH: And with the recent economic difficulties in the fall of 2008 . . . .

PG: Our current director, Dr. Niederhuber [John E. Niederhuber, appointed NCI director 2006] will continue to struggle with budgetary problems. The new Obama [President Barack Obama] administration wants to support science more, but it will be difficult because the country has a huge deficit.

VH: When I looked at your curriculum vitae in the early 2000s, the administrative milestones seemed more characterized by outreach than the creation of specific new programs,

which had characterized your early years at NCI. Would tell me about how you viewed the last eight years?

PG: Yes. During recent years, it has been harder to start things. That was because of budget restrictions and a negative attitude toward large trials. In the aggregate, we are not spending a lot on prevention trials. But when you look at the cost of individual trials and ask how many research labs the money for each trial could support, it looks like a lot. It really isn't large in total investment when you consider the benefits of doing the trials. Thus, lately we focused more on building on what we already had going, including the trials, and a much broader scientific agenda. This meant using the biorepositories and thinking about how to use things creatively and also how to build toward the future, using early discovery and development of interventions for the purpose of prevention. We also were aiming at engaging a broader part of the private science community so they would become interested in prevention, in training young people and working in networks all across the country.

VH: What do you mean by the private science community?

PG: Academia mainly, although we have a lot of clinical trials agreements with industry, but these are more often just for getting drugs, getting drug distribution, having placebos made up. We're not really working with industry scientists the same as we do with universities.

VH: In 2004, there was a symposium on bioinformatics and cancer detection, and I want to read you a quote from your remarks and then get you to define bioinformatics and explain its potential. This is the quote, "We should note two very interesting trends in biomedical research. First is the trend toward technology-driven rather than hypothesis-driven advances. Second is a greater appreciation of the need for integrative science. Molecular biology has been largely influenced by reductionism, the attempt to explain all biological processes by the same explanations as by physical laws that chemists and physicists use to interpret inanimate matter. Now with large amounts of data, we see the need for synthesis, understanding, and translational approaches, hence the need for aggressive development in the field of bioinformatics."

PG: We have many new technologies that have been coming online in the past decade, most of them developed by engineers and physicists and people in the engineering schools, such as MIT, Caltech, and Washington University. There are a number of excellent engineering schools. Most of the engineers came from disciplines outside of the usual biomedical disciplines. The institutions are getting more and more into biology and medicine, which is very interesting, and I think they should. We now have high throughput techniques for using tissue samples and genetics, analyzing molecular pathways. These techniques are moving us away from what's always driven peer review, where you had to propose a hypothesis and say how you're going to test it. We are moving towards the situation where we can get massive information and look at it observationally and see what we can make out of it, and that's going to drive where we go next.

These systems were set up to obtain and analyze masses of information--DNA sequences, proteins, and various other molecules. A lot of the resources of NCI have moved toward funding that kind of study, putting some pressure on the investigator-initiated pool of grants, which is kind of sacred at NIH. These studies also require more contracts, more cooperative agreements, more team science, because sometimes the engineers, even though a lot of them are quick studies, sometimes don't know the biology, so they have to work with biologists. We started gearing up for that.

The other thing that has happened is the ability to use large datasets in new ways. Take a trial, like an early detection trial, and say it works. The trial gives you several points of solid knowledge, but there are the in-between points that you would like to know about. You would like to apply the information to other populations or to population subgroups. Some of that can come through mathematical modeling. If you look today at the need to lower disease rates and improve efficiency of healthcare, a lot of that comes from outcomes-research modeling, modeling based on input from cancer rates from hosptials, population statistics, census data, and data from other health information systems. You can put that together and try to figure out how to optimize things, a massive computer integrative system. You have information technology at that level. You have a need for standardization. NCI has a computerized information system called Cancer Biomedical Informatics Grid (CaBIG), because people doing clinical work are not all using the same system, yet we need to be able to compare data. We are requiring data from all clinical trials to be entered into this system, because you have to know what's going on so you don't duplicate excessively.

Then we have similar approaches to modeling cells. Of course, you have to simplify what is known, put it into a computer system so that you can then see how to make an impact. Information technology is affecting everything.

I'll give you a couple examples of what we've done. In the Early Detection Research Network, which studies biomarkers, we are working with the NASA [National Aeronautical and Space Administration] Jet Propulsion Laboratory [JPL] in Pasadena, California. Why? The fact is that at NASA and the Jet Propulsion Lab support professors all over the country looking at huge amounts of information, and NASA has to integrate it and make sense out of it, much as we do with cancer-related data. We also have professors all over the country working on cancer research. NASA has an information-technology platform, their solar system platform. We felt that the work they were doing, this system of setting up their computers, was applicable to what we needed to do in biomarker research and to integrate the information from hundreds of sources in a way that you can look at and make sense out of it. There are scientists all over the place doing the work, and each is a collaborator in the system.

Next comes nanotechnology. Nanotechnology also means a lot of things. We're not deeply into it in my division, but in NASA, if you make something small, you can shoot it up in the air easier. Of course, we don't do that. Also, if you make a battery and everything's close together (via nanotechnology), the battery lasts longer. We use nanotechnology differently. We have groups that are investigating whether we can encapsulate a toxic drug and make it go to a tumor with monoclonal antibodies and open up when it gets there, using some of the same technology of nanotechnology. There are diagnostic test ideas using nanotechnology. But there are downsides that are not well

understood. You can muck up the environment in some instances. The nanomolecules might get in cells in a way that can be harmful.

VH: In October 2006, Dr. von Eschenbach moved over to the FDA to become its commissioner, and Dr. John E. Niederhuber became the new NCI director. Now, I know you've had some difficulties with Dr. Niederhuber, but would you comment on his priorities and his administrative style?

PG: Yes, there was some sort of problem at FDA with Crawford [Lester M. Crawford, D.V.M., Ph.D., FDA commissioner July-September 2005], who had to leave immediately due to a conflict of interest. President Bush then asked Dr. von Eschenbach to go take over the FDA, and John Niederhuber, who was here as a deputy to von Eschenbach, was appointed to run the NCI. He had been the head of surgery at Stanford and had run a cancer center in Wisconsin. He does some basic studies related to stem cells. He came in as a reasonable person to talk to one-on-one. His priority was more discovery and less clinical research. He seemed to want to put most of NCI's resources into early discovery and new technologies.

VH: Discovery meaning basic research in the lab.

PG: Basic research in the lab, yes. He also recognized, I think correctly, that there are a number of inefficiencies in our system in the way cooperative groups did clinical trials, and NCI had a program called SPOREs [Specialized Programs of Research Excellence],

which were program-project-type grants. We also didn't have an adequate handle on information technology. So Dr. Niederhuber wanted to deal with that. NCI wanted new initiatives on sequencing different types of tumors and using that information. Dr. Niederhuber came in to find a budget that was flat, things that he wanted to do and thought were important, and that did not include big prevention trials. It was a time when we had already sponsored a cooperative agreement with a group called NSABP out of Pittsburgh, a group that in my view is the best that's ever existed in breast cancer research, I would say *the* best in the world. The NSABP had done a breast cancer prevention trial with us showing Tamoxifen reduced breast cancer occurrence by half. They followed this with the STAR [Study of Tamoxifen and Raloxifene] trial.

The STAR trial showed that another drug called Raloxifene worked just as well in preventing breast cancer with fewer side effects, and we wanted to now test that drug against another class of drugs called aromatase inhibitors that we thought had the potential, although we didn't know for sure, but had the potential of cutting postmenopausal breast cancer occurrence by as much as 70 percent. With our encouragement, a grant proposal was developed by NSABP. It went through peer review. It scored wonderfully well in peer review. Niederhuber wanted to block it, because he wanted the money for something else, and he said, "It's not innovative science," something like that. Well, you never have innovative science when you're to the point of Phase III trials because everything came before, but Phase III trials are the final pathway to most progress against cancer. That's where people benefit.

My attitude was, for scientific reasons, that this was a very important trial to do. Many women could benefit all over the world. We needed to know and we did not know

which would be a better approach to breast cancer prevention or whether some women might do better with one drug, some with another, because the drugs have different patterns of benefits and side effects.

I also had an attitude about budgets that I think differs from Dr. Niederhuber's. I don't think it's a zero-sum game. Zero-sum means that if you spend money here, you don't get money there. Within the one year, that's true, but to me, if you have a flagship trial that the public relates to, that Congress relates to over a few years, they understand that that's a good investment and they'll support you. So if you say genomics, genomics, over ten years in a row and they don't see a decline in cancer rates, that's not going to help you build a scientific field. But if you do a trial that lowers the occurrence rate of cancer, support of your agency likely will be increased. So I was for this trial as a top priority for NCI.

After some internal meetings to which I was not invited because Dr. Niederhuber knew my attitude, the decision not to do the trial was made as a top-down, "I know better" kind of setup. We had a meeting of the National Cancer Advisory Board in June 2007, and I spoke up strongly for the trial, to Dr. Niederhuber's dismay, and there was retaliation after that which is—

VH: What kind of retaliation?

PG: Well, I would name three things. It's hard to prove but was quite clear. Number one, on my performance plan, which is called a COER, Commissioned Officer Effectiveness Report, he had Alan Rabson, his deputy director, write a mediocre report of my

performance. Alan had told me that he was doing it that way because Niederhuber wanted that. Well, that's inappropriate collusion between the rater and the reviewer. It actually would be grounds for grievance, although at my level I didn't want to go that route.

The second thing was related to our preventive oncology program, a training program that we were running. I'd wanted to modify the program to bring in physician-scientists and engineers familiar with the new technologies. So I wanted to change it. The guy running it under me didn't want that, because it would take a lot of his energy to go out and attract these people. Niederhuber then asserted that prevention is NCI-wide. He moved the program to OD [Office of the Director, NCI].

There was a third factor related to the breast cancer research. The trials I mentioned earlier were aimed at preventing the hormonally driven cancers, the 70 percent that are estrogen receptor-positive. We don't know how to prevent the 30 percent that are estrogen receptor-negative. So we were building a concept to get at that. Again, we wrote a proposal, Request for Applications. Niederhuber pulled it and asked for another committee to look at it, which he had set up. That initiative has been stalled for a couple of years, and it's in another division now, more or less, under Dinah Singer [Dinah S. Singer, Ph.D.], who was happy to usurp it. To me, it's unethical to obstruct progress because of some personal feelings.

VH: And what was the final outcome on the original trial that you spoke up for? Did it—

PG: It's never been done.

VH: It's never been done.

PG: The trial's never been done. No. We don't know and we won't know whether we can prevent 70% of post-menopausal breast cancer. It's a tragedy.

VH: Is there anything else you want to note about this?

PG: We've thought a lot about how to move forward in the future, and I think there are several directions. We have to build on lifestyle and public health approaches to prevention. It doesn't necessarily have to be my division. There's another group that helps do that. But it does mean working with other sectors of society. If you want to improve lifestyle, you may have to work with city planners so that people can exercise, can walk safely, ride bicycles, go to playgrounds without worrying about safety. You might want to work with restaurant chains. You might want to work with school systems. So you have to look at what influences people's behavior. In behavioral science, I think we have to work on the behavior of institutions and the behavior of policymakers, not just individuals.

We know historically what has had the biggest impact on health. Engineering has reduced infectious disease more than medical interventions. On the medical side, we have a lot of leads. It's just a matter of more resources. We know where to go. Of course we may learn more about where to go, but we know a lot of things that we could do that are potentially important. We have to find out what will work. We have a

number of clinical trials ideas aimed at cancer prevention. We know that we need long-term follow-up because that makes the trials more valuable, both for cancer, but also for looking at other conditions. We have basic resources, the biorepositories that allow the basic scientists to do their work more effectively. The cost of long-term follow-up has to be accommodated, but it's very hard when you're under pressure of a flat and essentially declining budget in real dollars.

My division had a retreat about what we are going to say to the next NCI director. If the President decides to make a change, what are our opportunities? We thought about that, and there are many, many opportunities. Some of it is integrated. It's not a standalone division anymore. There's a lot of integration of science and communication across disciplines that we're eager to build upon and to take part with our colleagues.

VH: In the last decade, you've been awarded numerous honors for your contribution to cancer prevention. Are there particular awards of which you're especially proud?

PG: I'm glad to get them, but I don't value awards so much as what I have been able to achieve with respect to reducing the occurrence of cancer, improving early detection that lowers mortality, and helping with public understanding of this disease. As I'm getting older, to try to give the glory to younger people. It gives them incentives. There are times when I've been invited to be on TV, where I'd ask someone younger to do it just because they get such a kick out of it and it means so much to them. It's fun. It's nice to get appreciated, but bringing along the next generation of physicians and scientists is more important.

VH: Historians are impressed by the awards that people have gotten, but what we really want to know is what did you do that led somebody give you that award? Tell me the details!

PG: To some extent it is related to the career I chose. If there's money in it, the private sector will do it. If there's glory, academia will do it. The rest is for us in government. But still we sometimes get recognized. Most of my awards were for creating and building the field of cancer prevention. Cancer prevention research—including clinical prevention trials.

VH: All right. Looking back on three decades here at NCI, can you tell me how you think the Institute itself has changed?

PG: The whole body of knowledge in medicine and science has grown tremendously. I'm sure this will continue to grow in the future. Science is far more global that it was in 1981 when I arrived. While I'm impressed with what's been accomplished, I'm concerned that the U.S. is slipping in its education system. We have some of the best of the best people, but they're a small proportion of the population. In a global world, a competitive world, although we like to collaborate, I think that we could do more to focus on the next generations and making them strong leaders. I'm optimistic we'll have progress against cancer. I think the research on applications is slower to take hold. NIH could do more to take responsibility to follow through to public benefit. This is not

sufficiently ingrained in the NIH systems. Of course, this should be done in partnership with other agencies and the private sector.

We have many opportunities across disciplines. We're set up categorically at NIH, by disease category. In prevention, there are a lot of things that impact more than one disease endpoint. Some of the things we're talking about, whether it's lifestyle or drugs, affect heart disease, affect diabetes, may affect cognitive function or other conditions—e.g., vision. We need a better way of working together across categories, in collaboration. When you have to go to every institute's advisory council before you can do one thing, you get stalled. They all look at, "What's in it for us," so you get stalled. So I think we have to think about the efficiency in our system and how to get a collaboration for the best public benefit. We haven't done that adequately at this point. But I'm optimistic about the future. We see all sorts of opportunities and they'll continue to grow.

We also have to do a better job of planning for succession within the NCI. I've raised with the NCI Executive Committee the question, "Shouldn't a Division Director rotate off every six years, take a sabbatical, and come back, but not as a Division Director?" That went over like a lead balloon. They gave me reasons why it wouldn't work in the NCI bureaucracy--how your job's tied to a supervisory pyramid, and we don't always have enough depth of FTEs [full-time-equivalent personnel positions] to have enough qualified people who could just take over while you are gone. We have many situations where one person is critical. It's hard to let them take off for six months or a year, but that would be refreshing. We're better at bringing people in for sabbaticals. We do that all the time. We have two or three in this division all the time. But it's much

more difficult for us to take our own staff and say, "Okay, you can go off for six months or a year and come back." We're just not set up that way, and neither is the entire NIH. I think that would be healthy, given the way the world's changing. In addition, we're making it a very difficult time for young scientists to the point where many of them will choose not to go into science because the rewards are uncertain and years and years away. I see people in their mid forties now before they get a grant of their own, and they have a tough time with housing, with raising their children, because we haven't set up a system that makes it easy and attractive.

VH: As we come to the end of this oral history, would you highlight the achievements of which you are most proud over your thirty year career?

PG: Number one is creating and building a field of cancer prevention essentially from zero, except for tobacco. Even with tobacco, what existed wasn't control; it was an attempt to discover what causes lung cancer. Building the field of prevention from nothing to where it's recognized across the world is my proudest accomplishment. I go to Japan and Japanese colleagues will say, "You're better known here than you are in the United States," because they understand the importance of prevention, and they've gotten into the field. So we have a field now that's taken hold, and it will last when I'm gone. We'll still have a field.

VH: That's my next question. Who will succeed you?

PG: I don't know, but I know there are a number of people in this division now who I feel confident could run a division like this, and there are some in cancer centers. But that number is small; I wish it were larger. I wish we could have grown the field even more. I think we have that potential, but it takes resources.

VH: Back to the achievements. You said number one was creating the field, and I cut you off.

PG: Then I would say number two, within the field of prevention, we built up the basic science of nutrition and evidence-based clinical and public health research. The medical approaches did not exist. We created the clinical field of chemoprevention. The idea from the lab existed, mostly from Mike Sporn and Lee Wattenberg, but the clinical field did not exist. We built that, and I think that will continue to grow. It's much like the heart disease comparison with cholesterol and high blood pressure--find markers of risk, bring down risk. I think the field of cancer prevention is now rooted in science, it's rigorous, and it will grow. It's not yet fully understood very broadly, even amongst physicians, so that has to take hold.

Many research centers have started to include an emphasis on prevention. We have cancer centers putting up prevention buildings, big ones, nice ones. M.D. Anderson [University of Texas M.D. Anderson Cancer Center], Fox Chase [Fox Chase Cancer Center], Seattle [Seattle Cancer Care Alliance], and others are the major centers. They are going to keep the field going. We don't yet have incentives in society in the way healthcare is managed that makes it easy to promote prevention. Prevention is sometimes cast as early detection, as something you can do with a medical test and

doesn't include the broader concept of how to reduce risk, improve health, improve quality of life. I think that's coming. I think we've started getting young people interested, but we've got a ways to go. It's not enough.

I think another thing--it's not cancer per se—is the fragility of our planet. It has become a big issue and is very important. It affects a lot of things, and sometimes people try to make the case for protecting the planet by using cancer, saying this or that causes cancer. I think that can be a lever, but that part is not usually proven to the extent that it's stated. The issues of planet warming and the increase of planetary pollution and population growth that affects quality of life, they're huge issues. Addressing them may help reduce the incidence of cancer and of other categories of disease and increase overall health, but that is hard to prove. We need to think of that for the future and for our children.

VH: Is there anything else that we should get on the record?

PG: I think you covered it. A lot's going to depend on the attitude of the NIH itself, its leadership, how it evolves over time. Advanced technology will certainly be part of that, both medically and in terms of economics. We have a huge opportunity for this country. We should stay in the lead and build on it.

VH: Thank you very much for a wonderful interview.