Dr. J Carl Barrett Interview

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Interviewer: Taping.

Barrett: Okay.

Interviewer: Could you start by telling me about your training and professional background, and how you came to NIEHS?

Barrett: I was trained originally as a chemist at the College of William and Mary. I then went to the Johns Hopkins University to do my graduate program in biophysical chemistry, which I got my degree in. I started in that area looking at nucleic acid structure, but was involved in a number of activities there -- carcinogenesis and in particular how environmental chemicals damage DNA to cause cancer. That then opened up to me the opportunity to get involved in doing cancer research. We started to do studies that looked at the ability of environmental chemicals to turn normal cells into cancer cells, and worked out some assays there. In the course of the studies I received my PhD degree in 1974. My thesis involved some studies where we looked at small oligonucleotides bound to DNA to specifically inhibit gene activity. These were the first experiments with what is now known as antisense technology. However, I quickly changed and got into the area of chemical carcinogenesis. So I stayed on for one year, which led to two years, which led to three years doing my postdoctoral studies.

In the course of doing these studies, we made some observations about how chemicals turn normal cells into cancer cells, but more importantly the mechanisms associated with the cancer process. We made the observation that this was a complex process. It was not a simple transformation of a normal cell to a cancer cell. There were, in fact, multiple steps in that process and I have spent the next 30 years trying to study those different steps and how that process occurs. My advisor presented my work at a conference and I happened to have breakfast the next morning with a fellow from Oak Ridge National Laboratory, Dr. Paul Nettesheim. We ended up having up a big discussion about my work and, at the end of which he offered me a job. He said he was leaving Oak Ridge to start a new laboratory at the National Institute of Environmental Health Sciences, this small place down in North Carolina that I was totally unaware of. I had several other offers but I went down and visited and thought it was pretty nice and so I ended up joining there in 1977, stayed there until 2000 -- 23 years. I came to NCI in 2000.

Interviewer: What was it about the NIEHS in 1977 that made it a compelling opportunity to you?

Barrett: First of all it was obviously an institute devoted to understanding environmental causes of disease and I had an interest in environmental chemicals as they related to cancer. Secondly, Dr. Nettesheim was the head of our exciting program. He was doing some seminal work at that point in the field of carcinogenesis and so the opportunity to work with him was very attractive.

Additionally, the chance to establish my own group and start to do this type of work was attractive. So a combination of the mission of the institute, the people that were coming there, which was Paul Nettesheim, in particular, and the opportunity for me.

Interviewer: Now, was that first group that you founded the Environmental Carcinogenesis Group?

Barrett: That's correct.

Interviewer: And how was it located within the institute? What was its specific mission?

Barrett: Dr. Nettesheim was recruited as a laboratory chief; he was the chief of the Laboratory of Pulmonary Function and Toxicology. He recruited me to be a Principal Investigator, and I chose environmental carcinogenesis as my focus. The laboratory had interest in pulmonary disease broader than just cancer. Nettesheim was a cancer expert and I was a cancer expert, so he recruited other people doing cell biology differentiation and lung disease types of things. But my focus was really to continue the work that I'd started with the mechanisms of carcinogenesis and how environmental chemicals influence that process.

Interviewer: And then in 1987 you became chief of the Laboratory of Molecular Carcinogenesis. Can you help me understand the trajectory?

Barrett: I came in 1977 and proceeded to publish a number of studies on mechanisms of environmental carcinogenesis. I received tenure about five years later. I continued to grow and develop in that area and started to receive outside offers of employment. The people at NIEHS wanted to keep me there, particularly the scientific director, was Dr. Marty Rodbell--who subsequently won the Nobel Prize for his work with g-proteins--offered to create this new laboratory environment of molecular carcinogenesis, so he promoted me into that position and I stayed.

Interviewer: And what was the overarching agenda for that laboratory?

Barrett: That laboratory was set up at a time when we were just beginning to get some first clues about molecular causes of cancer. I always took the perspective that there was two ways to look at the causes of cancer. One was the environmental causes, but the other was the molecular underpinning or molecular causes. Actually combining those two interests to try to identify the genes that are involved in the cancer process along with how the environment

impacted those genes, we thought was a compelling way. So the overall mission was to elucidate the genes involved in the process and use that information to understand how the environment impacts on it.

Interviewer: And at that time you said that this understanding, a focus on molecular mechanisms, was emerging. Can you convey to me some sense of what it felt like to be doing research in this area at that time?

Barrett: Well, there was a lot of excitement. Obviously, Bishop and Varmus, a few years earlier had cloned the first cellular oncogenes. Weinberg had cloned the *ras* oncogene, which was activated by chemicals and that was being studied by a number of different laboratories. There was a sense that this explained the cancer process, that we knew now the molecular cause of cancer. And that didn't fit with my notion that the cancer process was quite complex and there were multiple genes involved in that process. In fact, we had shown that if you had taken a normal cell and a tumor cell and fused them together you got a non-tumor cell. This was in contrast to the fact that you could take one gene and add it to a normal cell and make it into a cancer cell, which was a dominant effect. There were these recessive genes. But at that point nobody had cloned these recessive genes. Subsequent to that, people identified the genes that were what we now call tumor suppressor genes. But we had done some of the early work in showing that these genes existed, and in fact did some of the subsequent work in cloning some of those genes as well.

Interviewer: Was there ever any sense that focusing on the molecular underpinnings of cancer existed in any tension with focusing on environmental causes, or was it very easy to bring those two things together?

Barrett: No, it was very easy to bring them together. We were making advances on both sides. While we were doing the molecular analysis, we were also studying how a number of environmental chemicals worked. In particular, we focused on the class of carcinogens that were thought to be non-mutagenic. So I can take you back, both in terms of my history, but also the NIEHS history to tell you about that.

In the 1970s, it was recognized that many carcinogens could cause DNA mutations after being metabolically activated to chemicals. There were classical experiments by Bruce Ames, for example, that said carcinogens are mutagens. So it was a growing theory--

and this fit with the molecular identification of genes such as *ras* that could be mutated by specific carcinogens. So in some ways it all coalescing -- we recognized it in a naïve way, but at least at that point it looked like it fit.

The NIEHS had, from its inception, identified genetics as a key component for genetic damage and as being a component of environmental hazards. Scientists at NIEHS had done some of the early work in both carcinogen and metabolism, as well as in mutagenesis. Heinrich Malling was the one who worked out a number of the metabolic pathways with Jack Ben [sp?] and Jim Fouts. A number of the early pioneers of NIEHS had been involved in the metabolism, the pharmacology of chemicals and the activation of them, and they were beginning to study, in particular, heritable germ line mutations caused by chemicals.

There was not much of an emphasis in the early days, the first decade of the NIEHS, on cancer because there was a cancer institute. So there was, I think, an intentional focus away from cancer to sort of distinguish NIEHS from NCI. So with the recruitment of Nettesheim and myself, it was the first in-roads into cancer. When I established the Molecular Carcinogenesis Laboratory--that was the first carcinogenesis laboratory. So you can see the institute sort of grew into that. In between those two events, NIEHS had taken over the National Toxicology Program, which was a transfer from the NCI to the NIEHS of the carcinogen bioassay program, and so you can see there was a growing interest and involvement in cancer within the institute.

At the same time that I was recruited into NIEHS as a young pup, there was also recruitment of Jan Drake, who was a noted geneticist, and also Burke Judd, who was a very well-known Drosophila geneticist. So again, growing interest in the role of mutagenesis, and that's always been a foundation, I think, of NIEHS in the role of mutagenesis in disease--cancer being a very important example.

But nonetheless, there were these exceptions. At first, the Bruce Ames papers said that 98-99% of all carcinogens were mutagens. Increasingly there were examples of carcinogens that were not classic mutagens. So our interest in the early 1980's focused on that class of chemicals that were carcinogens but not mutagens, including hormones, asbestos and mineral fibers in particular, but a series of other substances as well. What we found was that these chemicals, while they did not induce gene mutations or point mutations, could damage the genome and cause genetic damage.

This finding included the hormones as well as the asbestos fibers. We went on to present a mechanism that explained how carcinogenic fibers were taken up by cells and caused chromosome mal-segregation leading to transformation. That is now a well-accepted mechanism in the cancer and the asbestos fiber carcinogenesis field.

And the same thing is true with the estrogens. We could show that hormones had the ability to cause malsegregation of chromosomes and transformation. That definitely occurs. However the relative contribution of that to other mechanisms in the hormonal carcinogenesis field is still debated. But certainly we provide other examples of how chemicals that were thought to be non-mutagens actually could act as mutagenic mechanisms. Additionally, we took a well-established mutagen that was unequivocally mutagenic with bacteria, and showed that it could cause transformation of the cultures. So we did the experiment in both directions to show that these were definitely causally related events. This fit very nicely and pointed us to identify the other genes and the mechanisms of how the chemicals worked.

Interviewer: And when you became the scientific director of NIEHS you maintained your leadership of the Laboratory or Molecular Carcinogenesis?

Barrett: Right.

Interviewer: What year did you become scientific director? Do you recall?

Barrett: What year did -- Tracy was there at NIEHS at that -- 1995.

Thompson: Right, because he stayed for five years.

Barrett: I was working my way backwards.

Interviewer: I looked for it and I couldn't find it.

Barrett: Oh, it should have been on my CV.

Interviewer: When you became the scientific director, what were you goals for the institute?

Barrett: I have to take you back a little bit, to tell you where the institute was at that time. The National Toxicology Program was created in 1979 by transfer from NCI to NIEHS. David Rall, who was the director at that point, recognized that this so-called testing program

-- which is what it was at that point, was just a matter of taking chemicals and putting them in animals and looking for effects – this was distinct from the research component, and so he created two separate divisions: a toxicology testing division and a intramural research division. That then grew into three divisions, when David Hoel, who was there, was made another division director, dealing with biometry and risk assessment. He was a cancer statistician. The institute was divided into three different divisions, which could have been three different institutes.

Interviewer: Okay.

Barrett: When Ken Olden came as director in 1990 or 1991 he recognized that this was a problem. Ken made some changes in the leadership making John McLachlan the scientific director. John made me Program Director--head of the Environmental Carcinogenesis Program, but I really served as his deputy in terms of helping to reorganize these different divisions. We merged together three divisions into one, all under the same scientific director, John McLachlan.

John was then offered a job at Tulane University and left. Subsequently Dr. Olden promoted me into the directorship of the intramural program. We had reorganized administratively, but we had not reorganized operationally and intellectually. So we were still very separate --it was two camps. Some saw themselves as the real scientists--who were the ones doing the basic research. And some saw themselves as doing the real mission of the institute--who were doing the testing of environmental chemicals. There was a lot of tension, you see.

Interviewer: Very well.

Barrett: There was a lot of tension between the basic research and the applied research, and my goal was to really make this a synergistic, interactive group and that's what I tried to do in the ensuing five years.

Interviewer: Okay. You've already spoken to this in some ways, but what were the challenges in making that happen?

Barrett: There was a whole series of challenges. Obviously there were communication challenges, there were cultural challenges, there were financial challenges, all these financial challenges, but mostly it was communication and cultural. People didn't see the value of working together and so there were a lot of educational activities.

Interviewer: When you look back on those five years what do you view as your most significant accomplishments?

Barrett: Well, I think we really did create one intramural program. And I think everybody recognized the contributions of others and they worked cooperatively and collaboratively to do that. We maintained a high degree of excellence in basic research that is without question but at the same time, we looked for ways to meet the mission of the institute and we looked for ways to do that in a creative new fashion. For example, at that time toxicology was a very descriptive phenomenological discipline, and we began to do toxicology on a mechanistic basis. I think that is still a work in progress, but it is very much the direction that toxicology needed to go -- it started at that point.

Interviewer: You're leading to exactly my next set of questions, which center on the development of three initiatives at the NIEHS that have been focused on genetics and on mechanisms and toxicology. The first is the focus of my research project this year, which is the development of genetically modified mouse models for use both in basic research and potentially as bioassays in the national toxicology program. I'm wondering if you can tell me if you recall when you first heard about the Tg.AC mouse or the p53 mouse and what your thoughts were about their role at the institute.

Barrett: We had developed a paradigm for thinking about how environmental health worked--that health and disease is a consequence of the interaction between one's genes and environment over time. We put forth that concept and it was accepted and developed. We used to argue about whether you get a disease because of your genes or because your environment. We argued it as either/or, but it was clear that it was because of both.

The concept of genetically modified mice—mice that were already one step along the process to disease and then being able to add environmental insults to the process-- fit very nicely with my entire career looking at the multi-stage process of cancer and trying to understand that. Additionally, we had shown that there were different mechanisms for chemicals that could affect the cancer process early versus late.

One of the chemicals that we had looked at was arsenic--a very well-known human carcinogen. The epidemiology is quite clear. The epidemiology says that arsenic induces cancer in a wide variety of tissues in the human population exposed to arsenic in

different ways, but it seemed to affect a later stage in the process. You can show if it takes 30 years or 20 years to get cancer. There is some chemicals that you're exposed to early and 20 years later you develop cancer. Asbestos -- it takes 20 years after your exposure to asbestos to get a cancer. So it acts early in the process. That didn't fit with all the mechanisms at the time that said asbestos simply promoted the growth of the cancer-- which would be a late affect. That's why we looked at the effects of asbestos to induce early changes within this genetic mechanism.

Arsenic worked at the opposite end of the process. It worked late in the process. If you were exposed to arsenic, five years later you get cancer, not 25 years later. So the epidemiology said it was working late. Arsenic is unquestionably a human carcinogen and there was no animal model. It was not carcinogenic in any animal model. That said to me that the animal models were wrong, and we really needed to have a better way of looking at these later effects. The animal models were starting all at the same time, 6 weeks of age, and going to two years. It was a very standard assay, which had its value because you could compare a whole series of hundreds of compounds. But it didn't necessarily fit the paradigm that different things operated at different ways. Phil Leder developed this mouse and showed that it was actually responsive to certain chemicals. It made sense to say, "Look at this and see if it would detect these chemicals that might act at a later stage in the cancer process."

Interviewer: As scientific director -- it may actually have been when you were working in the laboratory of molecular carcinogenesis, what was your role in nurturing this line of research?

Barrett: When I was made the head of the Environmental Carcinogenesis Program, which was 1991 or 92, Ray Tennant's laboratory was put under this program. I had known Ray when he came here from Oak Ridge and so I'd known him for the whole time he'd been there. He came to NIEHS in 1985 or so I was always a colleague and having inputs, but then when he was under my program I obviously got very much involved in his work and continued to support it when I was scientific director.

Interviewer: Looking back in the past, now almost 20 years of research with these models. What would you describe as their contribution to scientific research?

Barrett: I think the jury is still out in my mind. They afforded an opportunity to say, "Okay, we have a very defined genetic step in

the process and now we're going to look for chemicals that acted upon that genetic step." In the case of the P53 knockout mouse, which is another one that was developed and one in which I have a higher level of enthusiasm for the Tg.AC, that was exactly true. I think that has actually been a very useful model in trying to understand the effect of environment on genetically susceptible individual, or mouse in this case, and I think that has many examples where that contribute to our understanding of the effects of the various chemicals.

The Tg.AC is a very unusual mouse. It is a fluke. There was one of many attempts of this... It seems to be curiously sensitive to a variety of chemicals, but also to nonspecific injury -- wounding for example, and so I think there is something fundamental in why the Tg.AC mouse is susceptible, but I don't think we still understand it. And it's an artificial zeta-globin promoter in a particular orientation in the mouse that then gets rearranged with these chemical exposures to activate the chemical.

And I challenged Ray Tennant and still challenge him to sort of explain what -- exactly what is it. He has always had a bias that it is somehow something specific about the activation of the promoter to turn on the transgene that is the key event in the process. That may be the case, in which case you would say, "Well, it's such an artificial situation, what does that tell you?" And his answer is, "Well, it tells you a lot because there's all these data, these chemicals that work." Well, if you don't really -- you know, just because it shows a good correlation it doesn't mean it's really meaningful. It doesn't help you in the carcinogen evaluation mode. So to be able to show that phenolphthalein could enhance tumors in the P53 knockout mouse had a regulatory consequence. In the case of here -- okay, so you're going to tell me that I've got a chemical that's in my environment that turns on these zeta-globin promoter in this mouse that causes these papillomas. Well is that really something that I should worry about?

Interviewer: It's harder to translate.

Barrett: Yeah, I don't know. I think it can be looked at as a biological monitor and so there are some very nice studies that Ray did looking at benzene effects, which we know is a carcinogen. So the question of benzene is not is it a carcinogen, but what is the dose at which it is carcinogenic? So you can in theory get some nice data about dose symmetry and dose response curves, which I think could be useful in risk assessment paradigms. The quality of risk assessment, we don't know really what it means. My challenge to

him was, well maybe you've got the wrong mechanism. Maybe it's not activation of the promoter that matters, maybe it's survival of the cell once it's activated, and what your looking at then is some selective force that enables cells that have the activated *ras* to expand and grow into a tumor versus ones that do not. That would have a more generalized applicability in terms of understanding the cancer process and chemicals that influence the cancer process, because we really don't know what are the selective factors for the pre-cancer cells that are important.

They're going to be things that are important in developing cancer risk. And so we show, for example, that if you caloric restrict an animal you don't get as many tumors than if you've got animal that is feasting happily. This is a well-known phenomenon, but our contribution was that we showed that was associated with reduction of circulating levels of insulin like growth factor 1 and if we put back interestingly insulin -- IGF-1, to animals that where caloric restricted they got cancers. Furthermore, we showed that the reason was that if you looked at the tumors that were developing they were dividing at a high rate and they were dying at a high rate so there was a very clear balance between proliferation and death, but favoring proliferation, so you've got a tumor that grew. IGF-1 blocks cell death and is involved in cell proliferation, so we reduce IGF-1 by 25% -- it wasn't a big deal, 25%. Then you got an 8-fold increase in the rate of cell death and an 8-fold decrease in the rate of cell proliferation. So a tumor that's growing now becomes a tumor that's regressing.

Subsequent to that it was shown that IGF-1 levels in humans, 25% difference, can cause a 4-fold difference in the rates of breast cancer, prostate cancer, colon cancer, etc. So that is a generalized mechanism by which chemicals or environment -- in this case diet, calories, can increase your risk of developing a cancer in your lifetime or not developing a cancer. That's never going to be picked up in the traditional bioassay setting.

Interviewer: Right. Right.

Barrett: So I think that the transgenics can be very useful in mechanistic studies. I think you have to be careful in terms of using them for carcinogen evaluation and they certainly can be used for dose ….response studies.

Interviewer: Let me ask you about a second initiative, and this actually comes out of my conversation with Rich Sharp who suggested that I ask

you about the beginnings of the environmental genome project. Where the idea came from? How it got off the ground?

Barrett: The environmental genome project…so Ken Olden recruited Sam Wilson to the institute. You've probably spoken with Sam.

Interviewer: Quite a bit, yes.

Barrett: Sam was intrigued by the human genome project and said, "We should have a big project." So we sat around a table and we said, "What do you have in mind?" He just wanted a big genome project. So then we talked about the fact that there were these polymorphisms. We knew that polymorphisms were important in risk assessment, particularly for metabolism -- so we knew there was a 100-fold difference in the rates at which different individuals could activate different carcinogens, so there were at least differences between individuals, and that if we could determine the polymorphisms -- at that point there were a few polymorphisms known, and if we could determine that and create a database of these polymorphisms then that would greatly assist our epidemiologist. So the epidemiologists were looking for these low risk factors -- you know, in the general population they wouldn't see anything, but if you took, again, a susceptible population then you could get an effect. So the idea would be to increase the sensitivity of the molecular epidemiology tact and so that was the basis for the environmental genome project. So it really came from discussion between Sam and me and others to put this together.

We had a workshop. We had other groups that met to get input into this and then we had a workshop here at Natcher that sort of represented the idea. So I presented the idea to this smaller workshop that was -- Francis Collins was there and other members of the NIEHS community were there and there was a great deal of enthusiasm for that, and again this was a public forum, it was held in Natcher -- I forget the year that it was done, and subsequently were the RFAs and other initiatives that were started up.

Interviewer: '96' or 97?

Barrett: Yeah, it was around that time frame.

Interviewer: I have a conference proceeding from '97.

Barrett: Yeah right, that's probably it, in Natcher.

Interviewer: Were there specific technologic developments that made the project possible?

Barrett: Well the challenge, of course, was that at that time the cost of sequencing and identification of polymorphisms was quite high and so the estimates were that -- I forgot what, the numbers have changed so much -- $.50 per SNP to identify it, and that -- you can easily calculate to do this for all the genes you'd need, this would be a huge project. So the technological advances really came from the human genome project, which, obviously, was quickly developing ways to re-sequence -- obviously pushed the whole thing -- Francis Collins pioneered it, Jim Watson pioneered it, Francis Collins championed it and Craig Venter challenged it. Between the three of them it got done.

The sequencing of the human genome was focused on getting a sequence, not on getting all the polymorphisms and variations within the sequence. After this first workshop that we had -- first discussion that we had that was outside the institute, Francis said, "Congratulations NIEHS, you've really..."

But anyway, so the original idea would be we would re-sequence …specific genes, do this repeatedly with different populations, and we came up with different populations that we would look at and Francis subsequently took a similar approach. Obviously the sequencing of the genome by both the Human Genome Project as well as by the Celera group led to -- we went from having a handful of polymorphisms to having several million, and that's growing every day...

So I think the initial goal of the human genome project was to create a catalogue of all the SNPs. That's been achieved, more through the human genome project than through the NIEHS. So the next challenge is to use that information in epidemiology studies. That's harder, and it still needs to be worked on. That's something that we're doing here at NCI and they're doing there at NIEHS, I'm sure, but that still needs to be the future challenge.

Interviewer: When you started the environmental genome project what did you perceive as its risks and benefits for the institute?

Barrett: Well I think we recognize that its benefit was that we could do much better identification in humans of the environmental risk factors. Its risk was that we didn't know the size of the project and the costs were going to be very large, possibly. But I think it turned out to be not as costly as it could have been; and again,

partly because it became mainstream to the Human Genome Project rather than being a separate thing. And others recognized that this was important. So the sequencing centers when we started off were just gearing up, and so they obviously subsequently hit a very rapid pace of sequencing that we couldn't really anticipate in '97.

Interviewer: Let me ask you about one more initiative because I feel like we are probably running short on time. That is the development of a microarray center at NIEHS, which I understand was facilitated by your relationship with NHGRI and through your lab. So, if you would tell me about when you first heard about microarrays and the series of events that enabled you to bring them to the NIEHS.

Barrett: Well okay, so microarrays came on the scene, I forget now, the exact year that was -- with Pat Brown's discovery, and classical studies where he did this microarrays development. Jeff Trent had been very astute and had realized the power of this and had worked with Pat to sort of, you know develop this technology. At that point there were….it was all very primitive by today's standards. Jeff and I, colleagues and friends were working together on some other projects and he said, "This is a really good technology," and I said, "Geez, this could really be useful for toxicology." He said, "Well, we have this developing technology at our institute, we just designed our own arrayer." So he provided us the blueprints and so we made, I think, probably the second arrayer.

He had made the first one, it had an operational -- Cindy Afshari who was a fellow in my laboratory at that time -- postdoctoral fellow, I came to her and said, "This could be a very useful technology for lots of things in terms of basic carcinogenesis mechanisms, but certainly for toxicology." She went back and forth up here from North Carolina, learned the technologies. Jeff, Paul Meltzer, Jenn [sp?] were all extraordinarily generous and helpful to us in terms of doing that. So we developed our own -- we had our own arrayer built. It didn't work, there was all kinds of problems with it initially, but we eventually got that going.

At that point the great limiting step was to have a collection of genes, so our first thought was, "Let's design a set of genes that are specific to the toxicology field," so we developed the ToxChip, a postdoc in the laboratory, and Cindy and I sort of created this list of genes, we collected 2,000 or so different genes and created the ToxChip.

At the same time, Jeff, being at the Genome Institute, was interested in making bigger and bigger arrays, and they had 1-2,000 array chip at that point I think, and they thought they could go to 10,000. It was ridiculous. Nobody can make a 10,000. And, so that they didn't have the genes, so he and I split the cost of getting research genetics to develop 5,000 -- 10,000 for us, and then from that, he printed his arrays, and we printed ours. And so we then did, you know, 10,000 plus the 2,000, so we created a chip -- what did we call it at that time?

Interviewer: The Human Toxchip?

Barrett: The Toxchip was a 2,000, it was a very selective one. At that point we were arguing -- "You don't need 1,000, you can do it with 200. Why would you need so many genes?" Everybody was just starting this but thinking all small, they weren't thinking you could ever go to the whole genome arrays. So we created -- the Toxchip was 2,000 genes -- we called that the discovery chip, where we had 2,000 plus 10,000 random genes that we'd gotten for research genetics. And then we went off and we did the studies, looking at different chemicals as well and the toxicology.

We wrote a couple of articles outlining sort of what we saw as the potential for this, and the main potential obviously being to really get a [audio cuts out]

-- so this was a little bit overhyped. I'm to blame for that, but -- blame anybody else -- but it was a little overhyped as being sort of a replacement, or being able to do things that you wouldn't have to do with as many animals over a long term. In fact, I think the beauty of this is that this is really opening your eyes to all of the changes that are going on in biological systems. The thing about toxicology is that it's not, despite the fact that toxicologists have continually tried to look for easy ways to do assays, toxicology is the result of long-term exposures, of organisms to environmental [factors?]. And they adapt -- sometimes for the good, sometimes for the bad. But we don't understand this -- you give a chemical from 6 weeks to 48 weeks. 53 weeks, I guess, for the two-year bioassay. And you say, "Okay, after these two years you get this cancer effect." Well, all kinds of stuff is going on in between and we don't have any way to measure or monitor those changes. And then we're again trying to figure why this chemical causes an effect and this one didn't, and we're looking at all these little early changes, and there's a lot going on in between.

So to be able to actually look at this over time is a marvelous tool. And I think it's more empowering us to understand the mechanisms than it is as a quick fix of replacing some of the... The more you know, the better you are able to evaluate but you have to know a lot more and there's still a lot to be learned from using microarrays in biological systems.

I'm very pleased, I was just down at NIEHS over the Christmas holidays, and Gary Boorman came up to me and said, "You're dream is real. We're using -- in all our bioassays we're doing this now." So I don't know what they're getting, but they're certainly at least doing that, and I think that will in the end inform them about the process 10 times, 100 times, 1,000 times more than just simply measuring one endpoint at the end of two years.

Interviewer: So, you were there when the Microarray Center started;, and were you also there when they started the National Center for Toxicogenomics in 2000?

Barrett: Right. Cindy went and learned the new technology, we built the arrayer in my lab then she moved it out and we put the array in there and showed that it worked and did the proof of principle sort of studies, then was identified that this -- at that point it was beginning to catch on that this was important for others. So the NIEHS developed a RFA for the National Toxicogenomics Center, so all of those things were sort of evolutions of the original idea that we had about -- so it was a natural growth and progression. Obviously it brought in these outside people. So it was after I left that the actual center was codified --

Interviewer: But part of this stream of events --

Dr. J. Carl Barrett: It was a natural extension of what we were doing. And I had actually promoted Cindy to run the center and then we recruited Rick Paules to come to help do some of the toxicology stuff so she could do more of the mechanistic stuff.

Interviewer: He speaks so highly of you, by the way. He calls you a scientist's scientist.

Barrett: That's kind. So unfortunate for them but great for Cindy, she was stolen by….

Interviewer: Two more questions. I've been trying to understand the relationships, if any, between transgenics, environmental genomics and toxicogenomics. Is there any way that you would describe

these programs or initiatives as totaling a sum greater than their parts, or were these three distinct programs at the institute in a given period of time?

Barrett: They were part of a greater strategy of trying to bring new technologies and new concepts to bear in terms of environmental health sciences, and they really are extensions of the concept of gene environment over time. And obviously you need to develop animal models and you need better animal models to be able to do mechanistic as well as toxicological studies. So the bringing in of genetically modified animals to the gene-environment to question from the animal perspective was one thing.

To take that to humans you needed to understand what were the polymorphisms. We were in the process of identifying the major susceptibility genes. In 1994 we cloned the BRCA 1 gene, which was obviously a major advance. But it was clear that while these accounted for major susceptibilities, there were a lot of genes that had less effect but on more people. So the attributable causes are really much higher than the very potent genes that are in only a few people. So we needed to understand this environmental genome project to really understand how we could identify the gene component that mattered in humans.

And the third leg of that stool was the fact that we needed to look at lots of genes, and the new advent of the human genome project offered us the opportunity now to not look at one gene at a time, but really look at thousands and now tens of thousands of genes at a time. So I think they, all three, complemented each other.

Interviewer: That's incredibly helpful. Anything I should have asked you that we haven't touched on? Any pieces of this story that have gone neglected?

Barrett: Let me see. I have given it to you from the perspective of cancer, but the key thing about environmental agents is that they show no disease boundaries, so the same chemical that causes cancer could also cause pulmonary disease, Alzheimer's, etc. So one of the challenges to environmental health sciences is really to be able to look at all of these different diseases. We don't have the luxury of just studying cancer. Obviously we have a big institute that just studies cancer, but they have to deal with cancer and neurodegenerative diseases, and pulmonary diseases and kidney diseases.

So we need to have ways to look at technologies and readouts of biological systems to environmental, and then ultimately you tie that into the genesis of disease. So what this informs is the Environmental Genome Project, the transgenic animals in concept but not necessarily in practice, and the toxicogenomics, and really is not disease-specific. It helps us interrogate how environmental agents impact on biological organisms leading to the genesis of disease. So that's an important aspect of this, and I didn't want that to be lost. In fact, it's not just a cancer problem. It really is far greater.

Barrett: And speaks then, also, to the focus of the Institute [NIEHS] -- it's environmental science.