Dr. Kenneth Olden

Office of NIH History
Oral History Program

Interviewee: Dr. Kenneth Olden
National Institute of Environmental Sciences

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Beginning of transcript

Sara Shostak: Today is Thursday April 29, 2004 and I, Sara Shostak, am interviewing Dr. Kenneth Olden of the National Institute of Environmental Health Sciences.

SS: And you realize that I am recording our conversation?

Ken Olden: That's fine.

SS: Wonderful. Could you begin with telling me about how the NTP had evolved during its first ten or so years?

KO: I marked off the first three questions. I'm not the best person to answer the first three.

SS: Okay.

KO: But there are people around who could do that for you.

SS: All right who – are there particular people you'd suggest?

KO: Well, I would suggest a fellow by the name of George Lucier.

SS: I've interviewed him.

KO: And he used to work with us, obviously. He's very good and he was here from, if not the beginning – I think the beginning. So, he ran it and he has a good perspective on my era plus the earlier time, so he could do that.

SS: Okay, so let's pick up then with what sorts of challenges you perceived when you assumed the leadership of the NTP.

KO: Well, I thought that the NTP had done a very good job in making a case to the American people and Congress that toxicity testing was important to the public health initiative of this Nation, and I think they had done a good job in establishing a role for themselves – for the Agency -- in the health research enterprise of this Nation and public health of this Nation. However, I think the program – there was not a lot of innovation in the program. In other words, I think and I'm not sure you can ask people like Eula Bingham and some of those people about it who had a role in the development of the NTP, but at least as I look back I want to thank Congress in its wisdom felt that the National Toxicology Program should be in a science-based agency. And that the science from that agency should influence the conduct of toxicity testing.

I don't think that was occurring when I got there. I think NTP was – viewed itself as a laboratory testing enterprise rather than a science agency, and there is a difference. They were doing tests that were conventional, standard; and I think without intervention, and heavy-handed intervention, they would still be doing that. The NIEHS always, at least from the time I arrived, had very good intramural science; and since NTP is also an intramural program, you would think that there would be dialogue, interactions between the people who were meeting and participating in the NTP side and people who were in the NIEHS intramural science track, but that was not occurring. I didn't think there was any – or at minimal a synergy or interactions between the two programs and people – we were – NTP, for example, was contracting with scientific laboratories to do things, scientifically, to look at oncogenes and to do tests – to do real biology, to do biology and whereas we had scientists in the Institute who were far better, more knowledgeable, performing those tests and interpreting them than the contract lab. And so why were we paying and buying inferior science when we had it inside and we were already paying these guys?

And they wanted to do something more practical and more relevant and more immediately practical and immediately relevant than– you know the conduct of basic science is just that. It's basic science. It need not have practical application today or tomorrow. It is way down the road when finally somebody realizes that this little piece of this discovery made twenty years ago could be applied to develop a product, good or service or a treatment strategy, but that's a long ways down the road and basic scientists often don't think of the long-term. They just like the excitement of doing the science today.

So, I thought then, and I still think, there's benefit in getting basic scientists more in tune with the issues that we are facing today. So, that way they begin to think of the urgency of solving important public health problems. And I'm a basic scientist like that. I'm a basic scientist, but I don't want to just go in my laboratory and do fancy science and publish papers in great journals. I want to know that I'm really impacting peoples' lives; and I'd like to see it in either a public health prevention / intervention effort, as a public policy – in public policy or in clinical setting. I want my science utilized. I feel better about it and everybody – I think everybody essentially does.

I thought that was not the kind of interactions – and the opportunities didn't exist. There were firewalls and the budget – money is a big issue. The budget was distributed three ways in the intramural research program when I got there. It was – there was biometry and risk assessment was one division. Then the testing program, NTP was another division; and then there was the Intramural Research Program. So, let's say we had $100 million to distribute three ways, then the impact that we could have was far less, especially if those three groups didn't interact and talk with each other. So, I really felt that we should take all the money and put it in one place., $100 million or whatever it was, and say, "I want

to – the three groups you get together and talk to each other and let's plan strategically."

So, if we make a discovery in NTP, as I just had a meeting with Francis Collins; we're talking about mouse models. Well as I said to him, 36 years of NTP. Early on, what they were doing was we would add and describe. The science was descriptive and phenotypic in nature. In other words we'd add a chemical and we'd describe the results and we'd describe the phenotype, what happened, but we didn't know anything about mechanism. We didn't know anything about the genetic background of the animals and animal-to-animal variation in response - even in mice, there's something like 50 different strains of mice, and it varies. Chemical A would be carcinogenic in some strains, but not in others, and that didn't seem to bother anybody. But it is very important because if you generate data in one strain of mice that says this was a problem but not in another you don't know which is most relevant for human risk assessment.

There was no effort to try to attempt to define the genetic background of these animals to see which was more relevant to humans and that's what Francis Collins and I were talking about a few minutes ago and now we have a contract on the street to hire somebody, to take the 15 or 16 most commonly used mouse strains in toxicity testing and see what the genetic variation is in these animals, and see if we can see any correlation between genetic background and phenotype – in other words does genetics predict the pathology that we've seen over the years.

SS: That's fascinating.

KO: It is. That's the power of bringing things together and so – and the beauty of this is NTP people are at the table in this discussion and they have a lot to offer. We have 36 years of experience, of descriptive data. So, we know what the phenotypes are. We just need to know what the genetic background is and how can we bring those two together to improve human risk assessment, and the answer is, yes you can. So you have to make the investment to – essentially. Genetics is important and not just go down this pike forever and ever and ever testing some standard protocol. So, I think that's what I've done to the NTP.

When I got here I felt that we weren't looking enough at mechanisms. It's fine to say that chemical or physical agent A causes some disease endpoint or some toxicity, but if you don't know how it causes that endpoint then you can never intervene, you can never prevent the toxicity. Unless, of course, you remove the agent from the environment. Removing the agent from the environment was the NTP mindset – that was the thinking when I got here. That if we identify an environmental chemical, for example, as being carcinogenic or teratogenic or whatever then we will have EPA pass regulations to remove that chemical from the environment. And so that does – that will prevent the adverse health outcomes. But, in some cases, some of these products – take lead and mercury

and some of these agents, for example, automobile exhaust, we can reduce it but it's going to be a long time before we get many of these things out of our environment and the question is what happens to us, our next generation and generations after that while we're doing that.

So, if you understood something about mechanism, prevention and intervention would be possible even after exposure. Then maybe we could prevent the progression of diseases like cancer that develops over a period of 30 or 40 years, or if you just slowed down the process. Let's take prostate cancer. If you could just slow down prostate cancer to half the rate it is now, nobody else would die from prostate cancer. Thinking about it, you know, people die in their 80s now and you'd have to live to a hundred-and-something; and I don't know many people who live a hundred-and-something. So, you don't have to even cure things. You just have to understand and slow it down or prevent it. And so I think that is a much better approach.

Because the commercial products that we have in our environment are useful and they all were introduced with the expectation that they were not harmful. I mean the chemical industry, the pharmaceutical industry and other manufacturing industries - they didn't produce all these products to poison us to death. They were producing useful technology like the automobile. The automobile and the airplane, very useful, but there are some risks. There are some downsides. So can we have the airplane, for example, or the automobile or nanotechnology without the downside?

So, let's identify the risks. What are the downsides? And let's try to figure out what they are. What are the problems? And let's fix them. Well, otherwise we certainly set our society way back in terms of the economy, in terms of conveniences and quality of life. So, let's not just take one approach. I think that was – a myopic approach to how we prevent cancer is that we identify hazards, we tell the EPA, FDA and OSHA and they regulate. You just take that insulation out of your house, but at what cost in terms of energy waste and utilization?

SS: So, you undertook a significant reorganization.

KO: Right.

SS: Fairly soon after –

KO: Fairly soon.

SS: – your arrival. Can you tell me about that?

KO: Well, yes. When I first got there I went around and met with stakeholders. I have what I call an interactive inclusive management style. I like to go out and talk to the people, the stakeholders, whoever they are – whoever pays taxes are

stakeholders to me, and so I went out and talked to the American people – lay people. I talked to industry leaders. I visited DuPont, Procter and Gamble, and Dow Chemicals. I went to EPA and FDA and I talked to scientists and leaders of environmental and labor groups and members of Congress.

And basically what I was doing and saying is, "What should an agency like NIEHS/NTP be doing for you since you provide us with the resources? What are your concerns about your health and the environment?" And I heard. I listened. I learned that there were serious concerns; people were not uniformly pleased with the way we were doing business and that unless we did change we were running the risk of becoming marginalized. I think we were perceived as not being terribly mainstream and relevant, so we had to change. We had to incorporate modern science, take advantage of new innovations in cell and molecular biology and develop new test systems. As a matter of fact, it was in our mandate. We were just using a few very standard assays that had been in existence for years, and there are still people who tell me we should still be doing that. But I felt that we were not providing a very good product– a quality product; and the efficiency was very poor. In other words, we were spending too much money and generating very little useful information. There was not the synergy between the programs and we were not looking at mechanisms so you couldn't prevent except for behavioral modification.

And, so I made a decision to – I had some review groups to come in and look at our programs as well and they also supported my thinking. But I made a decision to take the three divisions and fold them into one and I didn't tell anybody, didn't give any hint about what I had been thinking. But I just walked in one day, in a conference room like this, where all senior leadership had gathered and said, "Guys, as of today we have one division in Intramural Research Program and you and you are out as division chiefs, not because you aren't doing your job, but you happen to be over the division that will no longer exist. As of today, we have one division so I can give the money to one person and hold him accountable."

And what had been happening, while I had been there a few months, I was going around and giving talks about-- we're doing this and we're doing that and we're going this direction and that direction-- and I would go back and talk to my senior leadership and charge them to do it. But, I'd discover six months later not a damned thing happened and I would go back and say, "well, guys, why didn't this happen?" "Well doctor so and so, he didn't like it and I couldn't get him to do whatever." And so I didn't know who to blame. And they all were – so finally I said, "Okay, fine, I'll stop that. You get the money and I'm talking to you and if you don't do it then I can do whatever I need to do to make sure that I get somebody here who can do it."

SS: Was that person the scientific director?

KO: Yes, I gave it to the scientific director. There was somebody already who was – had the title of scientific director and I didn't replace him. I just said, "You are the scientific director. Now you're the scientific director for the entire intramural research activity."

SS: And was that Carl Barrett at the time?

KO: No, that was John McLachlan at the time. John left a few years later and I made Carl Barrett the scientific director. So, that's how that happened and you can imagine--I mean-- all hell broke loose.

SS: I was going to ask.

KO: And I would say I wasn't sure I was going to survive more than – I mean they went after me. But Phil Lee was the Assistant Secretary for Health and that was when we had a real Assistant Secretary. In other words, the Assistant Secretary was a cabinet level position and it was approved by Congress; and so he was. And he had been the first Assistant Secretary for Health. So Phil was back, very seasoned, knew his way around and he stuck by me. He called me. "What are you doing Ken?" I told him what I was doing and I explained it just – that things weren't happening as we had expected and discussed and changes had to be made.

So I survived. But then there was an assessment later on in *Science*. *Science* magazine published an article called *Ken Olden Heals NIEHS' Split Brain*, brought the three hemispheres together. They went around and interviewed people randomly I guess, people who were leaders in the field. And I remember Bernie Goldstein, a very prominent leader said, "I was skeptical," and "I didn't think it would work, but my gosh Olden was right, it worked." And that was the general sentiment that it had worked.

SS: How long did it take for that [positive] sentiment to emerge?

KO: I can't remember. It took two or three years and during that time I caught hell because certain people would get together and write open letters to the editor and publish them in certain kind of little throw away newsletters and they would appear [_____] something magazine. And so they gave me a hard time, but finally that group disappeared. I mean they basically became converted and now some of them are my strongest supporters. So, anyway, there were people who would sign the letter, but they wouldn't sign such a letter today and they don't. Letters have been circulated out there, but they can't get the signatures now. I mean there are always one or two people out there who are never pleased with what you do if it is going forward.

But now those people are believers. They recognize the program is on the right track. I had the support of the NIEHS Council members. There is a lot of testimony on my council. Some people come back because they are recycling and

they'll say, "Look, I was here ten years ago. I was here the day Olden took over and I was here when all this happened, that is, when he reorganized the Institute. By gosh this place is totally different. It's much better." As a matter of fact, one of the candidates for my position was there and he just sings my praises now because he knew the Institute before and he knows it now. I changed it and he is excited about being a finalist for the position.

And so, I convinced people that we were doing the right things. Just yesterday I had dinner with friends, and while waiting for the husband to come home, I was reading the Washington Post and right there in one of the sections is a half page article on our children's longitudinal study that we are planning. Good press – NIEHS; we wouldn't have been there in the years '91 and before, because we weren't doing things like that. We were very narrowly focused on toxicity testing, and the institute was defined on the basis of cancer, first of all, and toxicity testing. Children's health wasn't on our radar screen. But I went in and talked to people and said this is our mandate and we should be addressing all of these important public health issues as they relate to the environment. So we created the children centers, and now we're collaborating with NICHD, CDC and EPA to develop this large cohort of children, because that's the way we are going to figure how the environment interacts with age and stage of development; we aren't going to do it any other way. So, we finally decided to bite the bullet and do it. So we've been sponsoring that effort. I was so proud to see the good press in the Washington Post – we wouldn't have been in there for toxicity testing, but we are now often cited in the press for a number of other good things that we're doing.

SS: You're getting press on that all the way into small town America, too, because my mom sent me a clip on the study from a paper in Fort Collins, Colorado.

KO: Oh, good. That's good to hear. And, you see, those kinds of things play well with Congressional people, we are proposing to expand the study to include parents and grandparents, and so it will be a very large family study and finally we will be able to say, after X number of years, by gosh, we have all the interactions, we can identify the crucial interaction between genes and environment that lead to human disease and dysfunctions and disability. But that's visionary. But you have to make the investment, and that's the kind of thing that we are doing now that is really putting us on the map.

I mean, this morning Francis Collins wanted us to have this meeting with him because he heard that we were going out and having 15 mouse strains, haplotype maps. Well, haplotype mapping of a mouse genome sounds like something Human Genome should be doing. But no, we should be doing it. He wanted to know why, so I sat down with two of my people and we explained it. Fine, he understood it. He thought we are going the right way that we are going to have a huge impact. And I said to him we were interested in this because we typically use anywhere from 15 to 16 different mouse strains to do toxicity testing. And if

you put a chemical in strain A, it may be carcinogenic, you put it in strain C or D it may not be. And we don't know why. Yet we regulate but we don't know that strain A is relevant to human risk assessment. What if the negative result in strains C and D were the most relevant? And everything is standardized, as I said to Francis, except the background. We can control the experiment. The only thing that we don't control is the genetics of this inbred strain. So there must be genetic variations among the strain; and if we know what the genetic variations are, then we can identify the causes of the phenotype variation. Why does it cause cancer in this one, and not in that one? And, there is a lot we can do with that information. So that's why we want this information. Francis could see that such studies are consistent with their mission.

And so, we made this argument. The meeting really went well; now Francis wants to collaborate with NIEHS on this effort. He had a little project, looking at a couple of things that could relate to it, but his is a million-and-a-half dollar investment and ours is 12 million dollars. So we will come in with wheelbarrow loads of good data that will help him with his small project. But you know, we left him with the impression that these guys are for real. They are players, and I have to take them serious now. I've got to talk to them. I can't just assume that all the genetics is going to be done in my institute or NCI. These guys know what the issues are and they are going to put the money up and they are going to be out in front and that was the message we wanted to leave.

SS: As a tiny bit of a side issue – is it harder to convince people whose focus on genetics – is on genetics, that there's also a role of the environment or harder to convince people whose focus is on the environment that there is a contribution made by genetics?

KO: I'm going to say – I'm not sure which is most – they're both stubborn. If I am going to guess, I would say it's been easier to get geneticists to think about environmental issues. Maybe it's easier to learn about the environment, and certainly the technologies and techniques are easier. Francis Collins, for example, is very into environment now. All he needs to figure out is a few little things; and we are working with him and collaborating to make sure they get that. But our people, toxicologists, or environmental health scientists, are reluctant to think about genetics because it's going to mean that they have to go out and learn new ways of doing things – I mean totally new. So I believe that it's my community that is most difficult to get them to buy into genetics – because I think that our community thinks – as I said earlier, you identify the risk factor and just remove it from the environment. But, there are a lot of environmental agents that we aren't going to be able to get out of the environment for a while. Francis Collins now uses the word gene environment interaction as much as I do, so I think that says something. I went to a planning – five year strategic planning-- for his institute, and he invited me because it focuses on gene environment interaction. Now, I believe that privately he thinks that genetics is going to be a bigger player. I don't think he's been fully convinced that the environment is as

big a player as it is, but he knows that he can't go forward unless he understands the interactions.

And I could tell you, I think the environment is going to be a major player. But in the end you need both, and the interaction-- that's key. But if you think of the contribution of the environment versus the contribution of genetics to any given disease, the environment's going to be the major – I mean two-thirds – you've got to have that environmental trigger and without it nothing's going to happen. And, I think people like Zerhouni have been convinced of it. By the time Harold Varmus left NIH, he was talking about gene environment. It's one thing to get the rhetoric, it's something else to feel it, and I'm not sure they have that yet internalized, but they'll get there. I think we're going in the right direction. As I'm stepping down, I just said to my Deputy Director, who is also a finalist for my job, that "this is going to the be an exciting time in the years ahead for environmental health scientists. You've got to work hard at it, and you've got to make sure you stay at the dining table, and you've got to – and stay in the thick of things, but it's exciting."

SS: And I hear that from the scientists I interview too, and I hear them talking – those who are kind of in the later stages of their careers – talking about how they're angling to stay in the lab a little longer than they would have otherwise because they want to be part of this.

KO: It's going to be a very exciting time. And I think the environmental part is going to get more money, because I just said this to Sam Wilson this morning, my deputy, as I showed him that article about the children's longitudinal study in the Washington Post . Well, we are already collaborating with Francis Collins to develop the next wave, the next large longitudinal study, which is the adult one, and the title is *Gene-Environment Interaction—The Family Study*. It is significant that the Director of the Human Genome Institute originated this study. So, we will be in the Washington Post and your local newspaper for that, too. And so I think it's a very exciting time.

But the challenges are going to be just as great in the years ahead. Visionary leadership and courageous will still be required of whoever comes in. The battle isn't over because, as I'll tell you, at NTP I think we've got a lot of work to do. I think I've got things started and I think I've changed the mindset, but there's a lot of work to be done because I don't think the interactions and coordination are as good as they should be. I don't think NTP has yet taken full advantage of all of the innovations in genomics and proteomics. Now you can understand why that would be the case because to get risk assessors to use technology or get data generated by some unknown technology, or technology that's different, that hasn't been, in their minds, validated, it's going to take a little while. So the policy applications that are going to follow are going to lag behind the science, but I think we're pushing it. I have commissioned two committees of the National Academy of Sciences to bring the scientific community together, bring

all the stakeholders – industry, regulatory agencies-- in one room, and let's begin to talk about how we're going to use genomics data in human risk assessment. And we need to do that now. Get the mindset, get people to think and talk about what science is needed before they would be convinced, as an environmentalist or as an industry executive, before they would say, "okay, you can use this." And unless we get these warring factions together to agree on something, five years down the road we'll have all the data, and I'll say, "By gosh, this is valid," and everybody says, "No, no, no, no, no, no. We've got to wait ten years." So we're having the debate now. So we're having the discussions and battles now. As a matter of fact, the Academy committees write a report after every meeting; and I can see what people are saying about his test or that test, and we can do the studies to prove or disprove whatever, and validate.

I think these new technologies are very important; and I am dissatisfied, let's say impatient, with the rate at which we are advancing the science in these new areas. All of these things are being incorporated, but I do see them – it is occurring. FDA, EPA, all of them are talking about how they will use genomic information. Yes, they're thinking about it; they're putting in place rules and regulations, guidelines to take the new science into account. So we are making progress, but we aren't there yet. We still need somebody to push the envelope.

SS: So, would you say that omics is among the most important scientific developments for the environmental health sciences?

KO: Absolutely, absolutely.

SS: Are there other developments or is that the premiere example?

KO: I think that's part of it. I think the other thing that I've done, and I think I've given credit for, and that is to emphasize the behavioral aspect of human health. I think the NIH has not put enough emphasis on behavior. And the reason for this, in part, is that those of us who become directors of institutes are laboratory scientists or clinicians, and very few of us are psychiatrists or behavioral scientists. Also, behavioral science, you don't have the objective measures of outcomes as you do in a laboratory or a clinic, and so basic scientists and clinicians object to soft science. But the application of laboratory and clinical science depends on behavior and even behavioral scientists. For example, if you develop a vaccine, which certainly is not a behavioral thing, a vaccine, it may work, but it won't work if you don't get parents, moms and dads, to take their kids to be vaccinated. And if only 50% of the nation gets vaccinated against something, an infectious agent, it won't work either. You have to have almost 100% compliance. So, in the end, you need people to buy into whatever new invention or technology you develop. So I think you may as well get people to buy in and vested upfront into the science. We don't need more laboratory or clinical research to prevent some health problems. Obesity associated morbidity is one example. So, we're taking on obesity and the environment – the built

environment, and we're co-funding a program called health living by design with Robert Wood Johnson now. We've got a study in progress. Well, you don't need a new pharmaceutical agent, you don't need to know anything about that person's genes. All you need to do is get a person to change their behavior.

SS: Which is more complicated than it sounds.

KO: Which is more complicated than it sounds, but you can do that, and we've got to figure out – certainly we can do pretty well with changing middle class peoples' behavior, but it's the other groups that we can't change their behavior. Not that every middle class person is going to change their behavior, either, but we do better with educating people like you and I. Probably neither one of us smoke, and certain habits we gave up or never took up, because we were told by our parents or our teachers, or we read in a newspaper or a magazine that it was not healthy, so we didn't do it. So we just have to figure out, though – and that's research – how to reach the other population. What is it we must do?

For example, we've contracted with a fellow who used to work with Sesame Street and Electric Company; and we are creating a show, a program just like Sesame Street, called the Fitness Fighters. We think the way to reach kids is through such television programs. All of my four children were influenced by these programs. None of us smoke. All of us are thin, and the youngest one was thin – and my wife and I just realized that she was thin as long as we controlled her, but now that she drives and goes to school and she's in a different setting than we are – and now she tends to be chubby. So we have to work on her constantly, because it's a matter of lifestyle, it's not genetic – it's a matter of lifestyle. So it can be done.

So, it's the preteen age group that we're targeting with this Sesame-Street like program. Fitness Fighters will use both animated and real life characters. So we think that we can make a difference. We are using TV as the means to reach them, but that's where they are anyway so that's where you've got to go. Also, during my tenure as Director, the Institute has begun to support community involvement in research, community-based participatory research, having confidence that people can make some decisions about what's important to their health and they can participate in research and you get them to get vested, to buy in to the research, so when the results come out, you'll have community people, non-scientists, going around talking to their friends to get them to change their behavior. And they can do a much better, effective job of that than you or I can – they don't know us. So, and the translation will be very fast.

SS: The uptake will be faster.

KO: Yeah, much faster. And so I think that's important. Health disparity, that's what it is really about. A poor black person or any poor person, any racial group; you and I don't have all this excessive morbidity and mortality, why should they? It

ain't genetics. It has to be cultural; it's behavioral. So let's change the behavior so they can have good health, and healthcare costs will go down and productivity will go up, and a lot of good things will happen. That's good. So we already know how to prevent a lot of things that we're not preventing. Obesity – we know how to prevent it. Lung cancer is becoming the major number one killer in women from cigarette smoking. Well, we know how to deal with that. We know the cause. But somehow we haven't stopped young girls from smoking and becoming addicted when they are in high school. So we have to do that. I think that's very important. I keep pushing NIH to do that.

SS: Now how do any of these innovations and directions, then, kind of integrate back with the mission of the NTP? How do you – is there a dialogue across?

KO: Yeah. Well – it's environment as we define it. The environment was defined too narrowly when I got there. Just the definition was so narrow. It was defined as chemical and physical exposures, mostly chemical. They almost never thought of physical, but they would occasionally think of radiation. But I said, you know, the environment's much more than that. The environment is your lifestyle choices. It is diet, nutrition, certain pharmaceutical exposures, and things like poverty – I mean poverty is not a genetic trait, it's behavioral or whatever. And so, we then expanded the definition; and I see it being used more and more by everybody. I wanted to be sure that when I went before Congress that they would understand why NIEHS was putting $10/$20 million into behavioral research, "Why are you doing that? That's not your mission." Well, as a matter of fact, I just got the question from the department about the built environment conference. "Why are you having this conference – this is HUD or some other agency's responsibility," and I said, "nope, the environment is – the built environment is a behavioral issue. We deliberately modified the environment in this way and so this is the environment." So I had to give them the definition of the environment and then their objection went away and Secretary Thompson wrote me a letter and said he would come to make a presentation, but originally there was this query — "this is not your mandate." Well, of course it was.

SS: David Rosner, who is a historian at Columbia, has a grant from Robert Wood Johnson now for a book on – it's called – the tentative title is *An Unnatural History of Public Health: Building the Worlds That Kill Us*. Which will –

KO: Yes. Right. Right. Exactly.

SS: – Lend itself to these sorts of arguments as well.

KO: Right. Exactly. And that's what we've done. If I was buying a house today I would go to a neighborhood that was people friendly. Where there were walking paths, trees and things so I could walk to the corner store – and I live in a neighborhood like most of other people. I live on a cul-de-sac and you can't walk in the street. That's it and there's no way to get to a grocery store except to risk

my life out on a major thoroughfare. And so, you know, I tend not to walk as much. But, I was just in Tennessee (I am a Tennessean) – they showed me a beautiful neighborhood with the most expensive homes and a walking path.

And it went for miles and people were using it, and that's what we're doing with Robert Wood Johnson. Their hypothesis is if we create environments where people can be active, they will exercise more. They are partnering with city, state and county governments to create some model neighborhoods. Now they didn't have money to do the evaluation. So, we are funding the evaluation part and the question is do you see more people out walking in such neighborhoods? You can count them. Do those people tend to be, on average, lower body mass? And so you can weigh them. You will see little kids riding cycles. They will be less obese or there will be less co-morbidity.

By redefining the environment, it's legitimate for NIEHS to deal with these issues and people see that it's more than just the synthetic chemicals. We didn't focus very much on the natural environment-- the natural chemicals – you know we weren't intended to eat all these things and so some of them are just as toxic.

SS: Let me ask you about the genetically modified mouse models because I want to make sure we touch on that today. You were at the helm of the NTP when these models were developed there. Can you talk to me about your perspective on that program?

KO: Yes. I've talked to Congress on two occasions about them and I think, let's say we're developing them at the moment for carcinogenicity testing. The two-year bioassay for carcinogenicity takes us two years to expose the animals, and it takes another two to three years to do the histopathology, to peer review and to report it out. So, it's five years. On average a test costs anywhere from $2 to $6 million per chemical depending on whether it's orally or by inhalation--$2 to $6 million dollars. It takes 800 animals. That's why I say, "it costs too much, it's too slow and uses too many animals, and in the end it's not very imformative."

KO: Not very informative, because all it does is give you yes or no answers. It doesn't tell you anything about pathway, mechanism, so nothing you can do to intervene or prevent. And I'll just give you one example. We determined in NTP during my time that phenolphthalein was carcinogenic. Well phenolphthalein was the active ingredient in some laxatives like Exlax, which was the most commonly used. It was carcinogenic in both males and female animals and in multiple organ systems but we didn't know anything about mechanism. So, we sent the data information to the FDA and they did what you would do. Well, they sent out an alert to physicians just alerting them that we had found this result, but nothing else happened.

Since the two programs (that is, NIEHS laboratory research and the NTP testing program) had been brought together, the NTP people just walked across the

hallway and mentioned this study to ask a couple of our geneticists would they look at it. In other words what did it do in terms of genes? Did it influence oncogene expression or alter suppressor gene functions? Well, we discovered that in a matter of months, not a year, less than a year, that phenolphthalein modified oncogene expression. We then sent that information to FDA and so now not only do we know it causes cancer, but we have a possible mechanism. With that information FDA had phenolphthalein removed from all laxatives. So, now there are no laxatives with this ingredient now on the market.

KO: – to the animal not very informative. So if we're going to test the universe of chemicals that we are exposed to, there are more chemicals to be tested than we could ever test given the cost and the time. And new chemicals are being made now so fast. So we can't even keep up at the rate that they're being made, so you have to have test systems then that are fast and cheap. We have made the investment to develop transgenic animal models that are more responsive to carcinogens.

Well, transgenics will identify a carcinogen in six months, not two years, at just a fraction of the cost. So, maybe then you could test many more chemicals, and it's fast and cheap and it's predictive. So we now use the transgenic animal models and the FDA will allow it, EPA will allow it. Well, they say you can substitute a transgenic for the standard mouse or rat assay, so we've already had a huge impact. You could say that we reduced the cost to industry, and to the government, to one half of what it would cost us to determine if something is carcinogenic.

So, if it's carcinogenic in one of the transgenics – and transgenic in the standard mouse or rat bioassay you've got it. So, we've already made an impact. But the idea was to develop a test system that was fast and cheap.

Now, something else that I hope I've changed is the thinking that a single test will ever be the be-all end-all. In other words, I think what we're going to be using in the future is a battery of test systems that are fast and cheap. And so if it costs only $100,000 to do three test systems, then why spend $2 to $6 million and wait five years if I can do this in a matter of two or three months. I'm hopeful that we can do this in a matter of weeks with time. So, that's the purpose in developing the new test systems.

I think the transgenics have already had a huge impact and I think we can make better ones. I think that's just a first generation of transgenics. So, I think that when we understand more about the mouse genome, which we're now beginning to do, the human genome, about the variations, which genes are responsible for cancer susceptibility; I think we can make better transgenics. So, I think that we have already demonstrated that better test systems can be developed.

So, we've already made a huge impact, but I think toxicogenomics is where the big excitement is. So, that's why I created a toxicogenomic center. I said, "Why use even a transgenic animal? Why wait three months, six months? Why can't we do this in one week?" Toxicogenomics, I think, is going to allow us to do just that. I think you can look at gene and protein and metabolite expression patterns. Now you can't do proteins so well yet. You can't do metabolites so well yet, but you can already do gene expression. We're going to be able to take those technologies and go into a laboratory and generate a fingerprint, a signature pattern, that is absolutely predictive of toxicity and that will happen within five to ten years I'd say we'll be able to do that.

I think five years we will be using them, some of them, because we've already done proof of principal studies so that we can differentiate between a toxic versus a non-toxic substance. We got a pharmaceutical – we meaning people in the institute, I didn't do it. Ray Tennant and his colleagues, they're partnering with industry groups, now it escapes me the name now, Ray Stoll who is at –

SS: Boehringer.

KO: Boehringer Mannheim, yeah. The pharmaceutical company sent us 23 chemicals, pharmaceuticals and we didn't know what they were. They just sent them to us and we were supposed to test them and see if we could identify them by class and say whether they were toxic or non-toxic. Well, I think we got 21 of the 23 correct. Now that is pretty good. So, it's going to work. It's just a matter of putting in place a fingerprint. It's like the FBI fingerprint database. If your fingerprint is in the database and you commit a crime and they get a fingerprint they can pick you out of a population of almost 300 million people. Well, we're going to be able to do the same thing from a population of 70,000 chemicals.

So, it is doable and we know it is doable. It's going to be as powerful as a DNA test, as unique, and if they get a sample of your DNA they could do the same thing. So, we're going to be able to do the same thing. It's going to be a signature pattern, kind of up and down waves, and right now it looks very complex and not doable but informatics can sort all that out and give you a very simple picture, and maybe the ones that are going to be predictive are just four to five little spikes. And you see those that is toxic. If you don't see them it's not. So that is the reason that I'm pushing toxicogenomics and create a toxicogenomic center.

Now everybody doesn't like the toxicogenomic center but it is the wave of the future. And, I hope the new director doesn't de-emphasize that. Whether this institute continues to lead the effort is uncertain because it does take money. I'm willing to chance my legacy to put the money the re. The NIH is a leader in science and that's what the American people expect of us. I mean we could elect, you know, industry – whatever his name was to clone the human genome, but we didn't. We kept scaling up the budget of the Genome Institute to make sure that

when we rolled out the human genome and the announcement was made that the director of the NIH and Francis Collins could be beside the President and we were – Craig Venter's group. So, we were there. Craig Venter was there, but we were there as well, because it was the combination of the two different approaches that got us the human genome project fast.

So, industry is going to do toxicogenomics whether we do it or not, but I want us to do it. I want NIEHS – NIH to be up front of that and when you say, "Where did the leadership come from on that?" That came from NIEHS. That's why we started – so…

SS: I know the pharmaceutical industry has been very active –

KO: Very active.

SS: – in that area. Has the chemical industry also been active?

KO: No, not as much.

SS: Okay.

KO: Pharmaceutical companies were already active for a different point of view because toxicogenomics is just a flip side of pharmacogenomics and they were interested in identifying targets for drugs. Also, they have to prove that their pharmaceuticals are safe and so it takes them five years too and costs them same as it costs the NTP. So, it costs too much and it takes too long. The bottleneck in pharmaceutical development is clinical trials and toxicity testing. And so they get 17 years of patent protection. So, if they could shorten – I've calculated that – so if they could shorten the toxicity testing by three years. Whoa, that's lots of bucks for a big drug. So, they can sell that drug to us under patent protection with three extra years that they would not if they had to spend five years in toxicity testing. And it's going to help with clinical trials, because you're going to be able to able to predict efficacy and you won't have drugs put on the market and then recalled.

SS: One of the reasons I'm interested in this is because that many of the same folks from the pharmaceutical industry who were collaborating with NIEHS to develop the transgenic mice are now collaborating around toxicogenomics.

KO: Exactly.

SS: What are the ways in which those initiatives are related? Did they build on each other or is it more a matter of personal networks?

KO: NIEHS didn't have collaborations with industry when I got there. The Institute was not partnering with industry. Industry was a dirty word, but I said, "That's

silly. Industry is in the same business we're in. I mean they need these test as much as we do, so why don't we go out and partner with them. At least we can use their intellect and their experience." So, I went out and identified about thirty industry people and invited them to come to the Research Triangle Park and meet with us. And, I pulled together the group around transgenics. And so we had them as natural partners and we had more than one meeting. So, they would come to RTP, we'd talk about partnering and how we were going to work together, so when we started toxicogenomics it was natural.

We continued those talks. I have gone to their meetings and had them at ours. We have had joint meetings. So, I think partnerships are very important and that's something – but I've caught hell from conservatives in our community, let me just tell you that.

The American Chemical Council is the trade organization representing the American Chemical Council. Well, we have a partnership with them and we co-fund grants. In other words, they pass money through to us and we fund the grants by the typical NIH peer review process and looking at the health effects of chemicals on development and they're interested because, you know, it's their product and they want to know is it safe and we convinced them to partner with us to do it and they did. But every now and then they hassle my institute with freedom of information requests about this or that. But it is the right thing to do because industry is part of America and they create jobs and they do a lot of good things and there's no reason why we can't maintain our independence and integrity at the same time have some collaborations.

We have to put into place safeguards to make sure that the interest of the public is protected. If industry is willing to give up all the rights and privileges – in other words, we call the shots. We say we're going to review the grant. We're going to fund it by our NIH standard and people can publish, there's no secrecy and they don't have to call industry to give them a six-month head start. These are typical NIH grants and you have access to data same way we do. Then if you can deal with that then we'll co-fund things. And so I am confident that the American public's investment is being protected. Well, unfortunately I've got to run.

End of transcript