Dr. George Lucier Interview

Office of NIH History
Oral History Program

Interviewer: Dr. Sara Shostak
Interviewee: Dr. George Lucier

Transcript Date: April 30, 2004

Prepared by:
National Capitol Captioning, LLC

820 South Lincoln Street
Arlington, VA 22204
703-920-2400

Sara Shostak: Okay, I think it's working. You know that the tape recorder is on?

George Lucier: I know that.

SS: All right. It's April 14th, I'm interviewing Dr. George Lucier of the National Institute of Environmental Health Sciences. My first question is if you could tell me a little bit about your background and training and how you came to NIEHS.

GL: Well I came here back in late 1969 as a staff fellow, essentially a postdoc position, and I came out of the School of Agriculture at the University of Maryland, which was an odd place I suppose to have someone come from to go to the National Institutes of Health. But while I was in graduate school I actually worked in insecticide toxicology -- that's why the association of the agriculture department. Actually, most of the toxicology departments around this country emerged out of the schools of agriculture because of the use of pesticides and the requirement that, especially at land-grant universities, give information to farmers regarding the safe use of pesticides, especially the new ones that were being developed at that time to replace DDP because of Rachel Carson's book, and so forth. So the long-last organochlorine pesticides are being replaced by the shorter, less persistent organophosphate pesticides, but these were more acutely toxic -- they basically were developed out of -- as derivatives of nerve gases that were originally synthesized during World War II by Germany. So most of the pesticides that are used on crops now are derivatives of nerve gases developed by Germany in Adolf Hitler's regime.

SS: That's also really interesting, because my understanding is that a lot of the original research on chemically-induced mutations was on gases that were developed for wartime uses during the second --

GL: Mustard gases and those sorts of things, that's exactly right. Now these pesticides -- sarin is basically a derivative -- let's say, used in part as a terrorist chemical that was used in --

SS: Tokyo.

GL: In Tokyo. That's an organophosphate pesticide. Most of the organophosphate pesticides have been chemically synthesized to be much more neurotoxic to insects than people, because people have an enzyme that can deactivate the ones that are used today. So even though they're similar in structure, they're -- when you eat your tomato or something you're not eating a great deal of potent nerve gas.

SS: Which is a good thing. So you came to NIEHS --

GL: In late 1960.

SS: To work in what lab and on what questions?

GL: This was the Laboratory of Cell Biology. Back in those days I was just hired by a lab chief and the lab chief said, "Work on whatever you want to."

SS: Who was that?

GL: This was Guy Owens. He left the institute in the mid-1970s. And I started working on different things related to organomercurial compounds, on the ability of the body to metabolize various environmental chemicals, which is similar in many respects to what I had done in graduate school. Later on I got interested in hormonally-mediated mechanisms and I got involved in receptor research; mid 1980's I became interested in translating that research that I had done, both in metabolism and receptors, to environmental health policy issues and to risk assessment. So I started a laboratory at that point called biochemical risk assessment -- how to use basic biological information to improve a lot of the uncertainties that were associated with risk assessment practices at that time and are still associated with it. And that's really how -- I suppose I got involved with the National Toxicology Program, and so I was hired as the director of the Environmental Toxicology Program in 1993, and as associate director of the National Toxicology Program mostly because I was interested in molecular toxicology issues, risk assessment issues and moving the toxicology program forward to take advantage of some of the newer tools in molecular biology that were emerging at that time and are certainly still emerging, one of them being the potential use of transgenic animals.

SS: So let's go ahead and talk about that. This is skipping ahead a bit, but that's okay. Let me start by asking how changes or innovations in the environmental health sciences find their way to the National Toxicology Program. Is it through collaboration, through -- either at the Institute or with academic partners -- how does that work?

GL: Well, what had happened with the toxicology program was that its centerpiece had been the chronic bioassay for cancer. That's why it was really formed -- to run these assays, to identify which compounds in the environment may cause cancer in experimental animals and to use this information to estimate what problems may exist for humans exposed to them. There was also the need to develop standard procedures for looking at reproductive and developmental toxicology, some of the non-cancer endpoints such as immunotoxicology. So the National Toxicology

Program became best known for its conduct of -- extraordinarily accurate conduct of traditional bioassays for various toxic endpoints.

This was fine for a number of years, but that's what -- how the reputation was built, i.e. the gold standard for toxicology resided in the National Toxicology Program. But as we learned -- this really began in the mid-1980's with -- sort of the coining of the phrases, "molecular epidemiology", "molecular toxicology". It became important to put that new information into the context of toxicology, research and testing. How can we use this new information to improve the way we conduct toxicology tests? How can we better generate approaches that would address the needs of risk assessment dilemmas, such as what is the dose-response relationships for different chemicals? How do we best identify sensitive populations, subpopulations, whether it be because they are genetically predisposed, whether or not something in their diet has predisposed them, whether some pre-existing disease has made them more sensitive or whether they're sensitive simply because they're a young child or an old person. The only way that this could be done is to take advantage of the new tools in molecular biology that were emerging, to apply those tests to toxicology testing and to compare what was seen in those tests with what was happening in people. Could we detect oncogenes? Could we detect toxic metabolites?

A lot of this really first emerged out of the disciplines of pharmacokinetics, in which scientists conducted multidisciplinary approaches, mathematics and pharmacology, to try to predict where chemicals and their metabolites would go, in various experimental cell systems as well as in people, and then to use this information to predict whether or not those particular exposure levels might be of toxicological concern. The next really big step was in the understanding that they were critical target genes -- oncogenes, tumor suppressor genes -- that played a key role in determining cancer outcomes in people and experimental animals, and whether or not it would be a rapidly advancing cancer or a relatively benign tumor that might never progress to a full-blown carcinoma or cancer that would pose a life or death threat.

This information was somewhat reluctantly incorporated into the toxicology program in the early 90's and I was keenly interested in doing that. There was some concern when I was hired as director of the toxicology program that I was just a bench scientist from the intramural program -- there had been a lot of competition between the intramural program -- the traditional NIH scientists and your National Toxicology Program -- two different classes of citizens, in some respects. I took it on as an important thing for me to try to develop multidisciplinary approaches, where it's the laboratory of scientists and the toxicologists work together. One of those areas was in pharmacokinetics, another one

of those areas was in "how do we apply information on oncogenes to the bioassay". It was out of that oncogene research that really emerged the idea of transgenic animals, because if you had a critical target gene that needed to be mutated before you got a cancer at a particular site on that gene you could then construct an animal that would already harbor that gene to see whether or not other chemicals could more easily kick it over the edge into cancer -- usually multiple genetic lesions required to produce a cancer. So if you already could produce an animal that had some of lesions or one of those lesions, you could determine whether or not chemicals cause cancer more quickly, with less cost, and also conduct more accurate dose response studies on tumor outcome.

SS: Who was involved with those conversations and what did they lead to?

GL: Well, the initial conversations were the oncogenes, and those were with Marshall Anderson, who's -- I don't know if you've heard of Marshall before.

SS: No.

GL: Marshall and I actually followed a similar career. We were both in a pharmacology department and we both had moved over to something called, at that point in time, the Biometry and Risk Assessment Program, so we basically jumped ship from the traditional NIH laboratory setting and said, "We want to apply what we do to risk assessment issues." We did this back in the late 1980s.

SS: And did you establish that program or did it already exist?

GL: No, we established that program -- that's what I said, the Laboratory of Biochemical Risk Assessment, I jumped ship from the Laboratory of Pharmacology and I was told not to do it by the then-scientific director, Nick Carter, and I took Marshall with me, one of the group leaders, Marshall Anderson. The director of the Institute, Dave Rall at that time, encouraged me to do this -- he thought it was important. So I basically did that and then tried to work back with the scientists who were still in the traditional laboratory setting. Marshall was the guy who did the oncogene work, and so we started looking at oncogenes in rodent bioassays and what genes were activated that were known oncogenes -- the Harvey Ras, these sorts of genes that then became -- these genetic lesions became the precursors for what was later developed in other settings, not here at the NIEHS, as transgenic animals. And when these animals became available, Marshall at that time was about to leave anyway, he took a job elsewhere in Colorado -- that's Marshall Anderson, and Ray Tennant then, who had been head of the genetic toxicology unit within the National Toxicology Program, became interested in applying these newly developed transgenic

animals to toxicology research testing. It really was an outgrowth of the Institute's interest in oncogene research that did that, and Ray, who had prior to this had basically worked on short-term tests for genetic toxicology to determine whether or not those tests were predictive of cancer outcome in the NTP bioassays. So he was a NTP scientist, so to speak, already.

SS: Even though his lab was in the DIR?

GL: No, not at that time.

SS: Okay, can you help me understand how those things were switching around?

GL: Originally his laboratory and his activity was in the National Toxicology Program. In the early 1990s it was moved out of the toxicology program because it was felt that all laboratory activities needed to be in the traditional DIR setting.

SS: So that's when the Laboratory of Environmental Carcinogenesis and Mutagenesis got --

GL: Yes, somewhere -- I don't have the exact dates, Ray would have the exact dates, but originally he was hired into the -- well, you're hired into the NIH but his work was primarily directed at National Toxicology issues and it was in what was then the precursor of the Environmental Toxicology Program, which was the Institute's way of coordinating the National Toxicology Program.

SS: Thank you. That's very helpful.

GL: Kind of complicated, but he was basically essentially an NTP scientist until -- I think it was 1991.

SS: Which is when all of the NTP labs got moved into the DIR.

GL: That's right, yes. And there was a period of time -- so there was very little from 1991 to 1993 -- very little activity in the National Toxicology Program as it relates to laboratory research here at the NIEHS.

SS: As a consequence of the reorganization?

GL: That's correct. That's correct. Some people liked it, some people didn't. Now at that time, I had moved my laboratory, as I said, out of the DIR into this Biometry and Risk Assessment Program, which --

SS: Which was a third entity?

GL: That was a third one. At that time, there were three programs -- the Division of Intramural Research, the Biometry and Risk Assessment Program -- so I was thrown in with a bunch of mathematicians and epidemiologists, and that's where I wanted to be at that point in time, to try to use mathematics, use epidemiology, use toxicology, use molecular biology to try to move the field of toxicology forward. Then there was the Environmental Toxicology Program, its precursor, which was mostly people who were running, coordinating the bioassays that were conducted elsewhere. So my lab, at that point in time, was sitting in nowhere land between the two with a bunch of mathematicians and epidemiologists. And that's how I met Chris Portier, because he was a mathematician, and how we developed our collaborations looking at new models to do dose-response studies.

SS: And that must have also been the lab into which you hired Bell?

GL: Yes that's correct. But then in 1993, when Bern Schwetz was leaving, I was asked to become director of the Toxicology Program. I was interested in doing it, and so I did that and started -- brought my laboratory in there, brought Marshall's laboratory in there and gradually started moving some of the laboratory activities back into the Toxicology Program -- I had a good working relationship with the scientific directors, at that time, John McLaughlin and then Carl Barrett. We had long time collaborators, we had a lot of mutual trust. So it helped diminish those barriers that existed between the two programs; a lot of people within the Toxicology Program were concerned that I was doing this. Basically it was a -- make this like any old DIR lab, but we tried hard to keep the focus on more applied issues within the Toxicology Program, and I think the transgenic issue is an applied issue. So Ray Tennant, although he was in the tradition DIR at that point, actually got a considerable amount of his resources from --

SS: From the NTP?

GL: Yeah.

SS: Can you help me understand how you saw transgenics at this time?

GL: You know, my view of it was in a larger context than just transgenics -- not only me, but a lot of people -- John Bucher, Ken Olden when he came certainly was very enthusiastic about developing alternative models for toxicology. And it's out of that interest that we formed ICCVAM, the Interagency Center for the Validation of Alternative Test Methods -- it was an interagency group that worked with FDA, EPA and others. It was clear that, because of the cost and uncertainty associated with long-term

bioassay, we needed to find better ways to do this more quickly -- not that we wanted to fully replace the traditional bioassay, but there had to be other ways that we conducted toxicology tests. Ray, of course, was interested in the transgenic issues, as were others. So we sort of pushed that in terms of providing resources to test chemicals that we're already testing the bioassay to see whether or not -- what kinds of responses we got in the transgenic animals. But the ones that were developed that Ray used were the TGAC, which is a Harvey Ras dermal application apaloma [spelled phonetically] model, and the P53 deficient model. So we would run a lot of the same chemicals in the two-year bioassay that we would in the transgenic tests to see what the results were -- what problems we might have, we conducted some dose-response studies that are fairly significant with the TGAC, with dioxin and dioxamide [?] chemicals and those kinds of things. But nevertheless, I viewed it in a larger issue. I didn't want to put all the baskets for alternative tests -- all resources for alternative tests into the transgenic basket. So we were looking at other kinds of things, and it's really a -- which now is part of the National Center for Toxicogenomics -- the gene array approach is, again the oncogene approach is where you just look for the mutations in animals. We did a lot of work with the receptor-mediated pathways -- how can we identify in particular changes in gene expression that would be a result of either dioxin or estrogen interacting with their receptor.

SS: This is Ken Korach or -- among others.

GL: Yes, Ken Korach, and what Chris Portier and I did, we basically modeled that kind of data -- we generated for dioxins, Ken generated for estrogens, then we would model it in the mathematic models. So the transgenics were important but not the only thing, and I think that remains true at the Institute today.

SS: So let me ask then about lessons learned during the experience of developing these models, and what you think their future is at the Institute.

GL: Well you know whenever you have something like this, the tendency is to be too much in a rush -- it's easy to get overconfident, it's easy to overpredict how soon you'll have information that can be used in either the risk assessment or toxicology arena. And that certainly happened with the transgenics, it certainly had happened with the oncogene, and the same thing is now happening with the global gene array. People say, "Oh my God, we have this new technology, we can instantly apply it to toxicological problems." And whenever this happens, the inevitable difficulties, the unforeseen circumstances arise that, "Oh my God, we just can't do it as fast as what we would like." I believe, and I think most people believe who look at it critically, that the transgenics offer

tremendous opportunity to look at classes of chemicals, to look at dose-response issues, to perhaps identify sensitive subpopulations.

That doesn't mean there's a cure-all. What do you do when you have a situation where you get a different result in a transgenic than you do in a long-term bioassay? Does that mean one is wrong and the other is right? No, it doesn't mean that at all. It means there are different experimental circumstances, so what I think people have come to realize is that you have to identify -- you have to define the question you're asking, then critically evaluate "what is the best experimental system for me to use to answer that question?" It may be a transgenic, it may not be a transgenic. They're not going to be useful for everything. They're not going to ever fully replace a long-term bioassay or partially replace it. I think you have to look at transgenics, is there some sort of metabolomic system I can use that will answer this questions, is there some sort of other test that I can use? It might be a blind shrimp, it might be some other system like that.

So it isn't going to be a case where every chemical the National Toxicology Program is interested in is suited for evaluation in a transgenic. Many of them will. The important thing is to define the question and to see whether or not that system will in fact help you answer it, and whether or not it's appropriate. The more we understand how those systems work, the better position we'll be in to determine whether or not they're appropriate. I think that's a lot of people are doing now. After this initial burst of enthusiasm, you're saying, "Well, we gotta really find out how this works. And I think when you talk to Ray Tennant I'm sure he'll you we're trying to understand that. We're trying to understand all of the molecular seculari [spelled phonetically] that are important to a transgenic response.

SS: Which is why there are now experiments going on with transgenics using the focal gene arrays simultaneously?

GL: Yes, that's correct. That's correct. See what is it that really is different about them that might -- and once you have this tremendous database in hand, about what the normal response is of a transgenic and what governs those responses, you then can ask those questions: does this particular chemical -- something that you might expect a response in a transgenic.

SS: So, related to what you were just saying, since the '80s and possibly beforehand, toxicology as a field has been under a tremendous amount of pressure to become more mechanism-based. How has this been important to the research undertaken by the NTP?

GL: Well you know, there's several associated questions with that. There are traditional toxicology tests reviewing, appropriately so, is limited, because

they gave you a simply yes or no answer. Does something cause cancer or does it not cause cancer, and what is the site at which it causes cancer in animals? Very little information was generated of value to determine at what exposure level it might be safe for a particular chemical. We knew that this might be a problem under some exposure circumstances, but what is the shape of the dose-response curve, what happens at a lot lower doses? Can we draw a straight line or some kind of crooked line to estimate that risk? And by understanding the molecular sequence of events that are involved in, say, cancer development -- the same issues are true for other toxic endpoints like reproduction, development, immunotox -- if we can understand the molecular sequence of events, we can do a better job of predicting what will happen at low doses, because if we know that these gene pathways are important, they're altered in a linear way as we go from high dose to low dose, this is a critical event in the toxic response we're looking at, we can then say with more confidence, "I think this particular exposure level in people might be at risk." Likewise you can say, "I have a rat model. How do I know where it is relevant and not relevant for estimating human risk?" If you understand in that animal how the chemical cause cancer, you can then say, "Does that same mechanism operate in people, and would it operate in the same quantitative relationship, in terms of producing that cancer?"

So then you can go back and forth between the human data, your animal data, and address the issues in risk assessment, which were really becoming quite controversial in the late 1980s and still are. How do you use animal data to estimate human risk? The environmental advocacy groups will say, "Don't let us be exposed to any level. If it causes cancer at some level we shouldn't be exposed to it at all." The industrial supporters would say that, "It's only at very high doses that this happens, we don't need to worry about our products, because they're safe at the doses at which people are exposed." So you're really addressing those questions by applying molecular tools to the field of toxicology. You're trying to give those risk assessments -- those policy makers, public health advocates -- more or less confidence in the models that you use. Which doesn't mean they won't still be controversial and there won't be the arguments from industry and public interest groups, what's safe and what isn't. But at least the risk assessor looks at it objectively, will have a better foundation at which to make those estimates, and will not have to solely rely on default safety factors to make those assessments. If you have no information on whether or not people are more sensitive than rats, you have to assume they are more sensitive.

SS: And these are ten-fold extrapolations?

GL: Yeah. If you have no information on whether children will be more sensitive than adults you have to impose extra safety factors to account for

that lack of knowledge. And this uncertainty is what causes most of the arguments of the risk assessment arena.

SS: So is it fair to say that toxicology -- the development of the field of toxicology is driven, on the one hand, by innovation in science, the availability of new tools, and the other hand its uses in arenas that have become contested and politicized?

GL: Yeah they've been politicized, and they're difficult, legitimate policy issue questions.How much does it take to produce a toxic response? The regulatory agencies of this country and other countries have a responsibility to protect people from unsafe exposure levels to chemicals. But the question is what is that level? And traditional long-term bioassays for cancer are not going to give you that information in most of the circumstances. They can in a few like asbestos and [unintelligible] because the response is of such magnitude, but in general they can't do that. Unless you provide molecular information to a company, those cancer findings allow you to better estimate at the lower dose exposures what might happen.

SS: So in part -- you referred earlier to the translation of science for uses in risk assessment, and I think you're talking again about how translation is done. How would you describe the work of translation? With whom are you in conversation, and how do you bring information to the regulatory agency?

GL: It's hard, it's hard. People with good reason like to have their arena that they work in, the people they're comfortable working with, where they have a great deal of expertise or knowledge whether it be in endocrinology, whether it be in -- the newest instruments for detecting toxic insenimar [spelled phonetically] and various gases, chromatographic methods and these sorts of things; people like to feel comfortable with their own. So there always has been a great deal of talk about multidisciplinary research, but often it doesn't work because people don't really move their minds to get in the other person's head. A mathematician thinks a lot differently than a biologist does, and every now and then you get synergies that occur between different people, so there are a lot of different success stories where this has happened.

But to translate the basic information into risk assessment, you really have to get in the head of the risk assessor, the policy maker, the toxicologist, because all are involved in this and if you can't do that it's not going to work. You can't just talk the translation game, you've just got to get in there and do it and try to understand the other's perspective. It's no different than any kind of interactions that people normally have if a husband and wife are fighting. The only way that those issues are

resolved is you have to understand the other person, you have to be in the other person's head and look at it from their perspective. "What is it that they want to get out of this relationship", not just "what do I want to get out of this relationship". And people often -- that's why you have so many marriages fail, that's why you have so many multidisciplinary research efforts fail. Why is it often done enough? So it's not just enough to go to the marriage counselor, you've got to really work at it.

SS: How did that play out around the transgenics issues?

GL: I don't think it turned out that well. That doesn't mean I'm negative thoughts about the future. I think there's a lot of territorialism involved in it. The pharmaceutical industries wanted -- they had their own set of questions that they had. The basic scientists had their own set of questions and they didn't want the field of molecular biology tarnished by risk assessors and toxicologists, never mind policy makers. The industry folks were fearful of how this information can be used against them. The environmental advocacy groups were fearful of mechanistic research because they felt that it would be a way of industries escaping regulatory controls by falsely saying that their chemicals were safe, by rigging the system to not respond or something like that. So there was a lot of paranoia out there and it takes a long time to work through. I think we're still working through that.

SS: I still hear some of those concerns when I interview people.

GL: Progress is being made, but it's slow and that's one of the reasons it's slow, is because there's a certain amount of distrust, there's a certain inability to get into the other person's head to see where they're coming from. And so it's not surprising it's slow. Scientists are like people. They are people.

SS: They are people.

GL: But they're not going to act any different. They may view their cause as being a noble one, and it is; that doesn't mean that their heads are all screwed on right, and it doesn't mean that they don't have their own egos.

SS: You mentioned scientists fear that molecular biology could be tarnished by risk assessment, and you said something earlier about different classes of citizens of scientists. Can you elaborate on that?

GL: Yeah, when I first got involved in the Toxicology Program -- remember I came from a Division of Intramural Research background here at the NIH, but it was clear that the toxicologists didn't trust the basic scientists, the basic scientists thought the toxicologist was taking away that was rightfully theirs. So there was --

SS: Competition?

GL: Competition, and competition's not bad. I think out of the competition, creative energies and synergies can happen and that it does happen, and I think there's some examples of that. So all I was saying is that the basic scientists would say, "I just want to understand how this gene works. I want to understand in a very narrow sense how my system works, what my interests are. I want to interact with my colleagues and move this forward in a very molecular, scientifically sound and credible way. What would happen if the toxicologists got a hold of this, or the risk assessors? They would use it inappropriately. The basic scientist who deals with certainty -- something has to be close to 100%. The toxicologists say, "Well that's not true, maybe 90% is good for me." And the policymaker might say, "Well, maybe 80% is good for me, because I have to make a decision. I have to make a decision on what's safe, I can't wait until all the information is in, so I want to use your system now to give me 80% confidence of what my decision is for safe exposure level." But the basic scientist will say, "Well, there are potential problems with using this. I don't understand this, this, this, this." The policymaker would say, "Well, if I waited to fully understand something 100% I would never make a decision, and as a result I would be a failure as a policy maker." Scientist says, "Well if you use this I'll be a failure as a basic scientist, because there are a lot of things I don't know about this system." And that's what I mean about the tarnishing.

SS: Okay. What --

GL: Legally, by the way, 51% is good enough.

SS: Oh I didn't know that.

GL: Yes.

SS: Must make scientists' skin crawl. When the NTP was established, it inherited the NCI's Cancer Bioassay Program. And at the same time, it was charged with developing new toxicological tests in the founding documents. I'm wondering how the NTP has pursued this charge to develop new tools and how it shaped the program.

GL: Well, I think one of the first things that the NTP did -- I was not involved in it at this time, Ray Tennant was -- that was to take genetic toxicology tests and apply them to the chemicals of interest. In other words, that was a mechanistic test.

SS: And that wasn't done by the NCI?

GL: That's correct.

SS: Okay.

GL: It grew out of the knowledge that there were critical mutations that occurred in target genes that might be responsible for the carcinogenic actions of some chemicals. This was work for [N.] Bruce Hanes and others back in the '70s. So the NTP, which was formed in 1979, then took advantage of these tests, and started applying them as a correlate to the

NTP bioassay. And so I think the feeling of it -- and by the way, during those days I didn't know what the NTP was or I didn't really care. It was only later that I began to care about those things as a scientist.

SS: When you became interested in risk assessment?

GL: Yes, back in probably the mid-late 1980s. Up to that point I could care less about what the toxicology program did -- didn't really know what they did.

SS: And you didn't interact with them either?

GL: Didn't what?

SS: Didn't have any significant interactions?

GL: No, did not. That changed very fast for me later. [laughs] That's when I became their bosses. But I did have a real strong interest at that point in time to do that so I was very happy I got the job. So I think, at that point in time, that's what they did. And then I think there got to be an interest with pharmacokinetics at that time -- how does a chemical move through the body? So they developed programs in chemical disposition. Skip Matthews, I don't know if you've talked to him at all, he probably wouldn't be too relevant for transgenics but he was very relevant to the issue of target-tissue dose. How much chemical did you get… that was -- I'll probably have to leave in a few minutes anyway, the kids are probably getting… I should check on them.

SS: You want to check on them?

GL: Let's see, where were we?

SS: You were talking about developing new tools within the NTP as part of the NTP's mission.

GL: Yeah, with the pharmacokinetics and chemical disposition. And then the next thing was sort of the oncogenes, and using the oncogenes we talked about then it became the transgenic animals, and then the global gene arrays, and proteomics and metabolomics. And overlaid all of that was the development of biologically-based models that translated all that stuff into mathematics, and that became my true love here, working with Chris Portier in taking all that basic information and putting it into mathematical constructs so then we could predict what might happen outside the range of experimental values. So I guess what I was saying that this was a sequence of events, I think that that have served as benchmarks for how basic biology is incorporated into the toxicology program. So it's occurred at a regular basis. It also occurs generally at some point after those findings have been made, the basic biology findings, because you can't just take every new advance that comes in and willy-nilly apply it to toxicology. This needs to be evaluated, needs to be looked at by a number of people with different perspectives, so it takes time. It doesn't mean we shouldn't try to address it, but we shouldn't try to rush into it too fast

either. Not every new scientific finding is correct. So we don't want to design new toxicology tests with incorrect information.

SS: It also seems like the NTP is in an interesting situation because on the one hand there's a strong desire to develop new tests faster, better, cheaper ways of doing toxicology, and on the other hand your stakeholders require validated, reliable forms of knowledge. How is that tension mediated or balanced?

GL: Well, the best way is to have all of these different parties get together and work out an agreement that's agreed to by all that addresses everyone's concerns. Sometimes the concerns are based on lack of knowledge and these sorts of things. So there's no substitute for people really getting together provided they have a sense of good will when they get together. You get together with someone who you simply view as an adversary and you're taking an egocentric territorial approach, it's not going to work. You have to get together with a sense of good will; there's no substitute for it in those sorts of discussions. I've been involved in a number of them because I've been labeled as someone who understands molecular biology, toxicology, risk assessment and public health policy and I've worked in all those different arenas, and so I've been involved in a lot of these negotiations. Some of them work, some of them don't. The only time they work is when there is that sense of good will. So selection of people to work with on these issues is very important.

SS: Two more questions and then I'll ask you what I should have asked but haven't yet. When you became director of the Environmental Toxicology Program, assistant director of the NTP, what were your goals and visions for that program and how did you pursue them?

GL: I never viewed myself as a visionary, I was always had short-term goals, and out of that, I think I always felt confident that you'd have long-term success. But what I wanted to do most of all were two things. One was to bring, in an orderly way, basic biology into the National Toxicology Program and it had to have, to do that, a basic laboratory component. So I wanted to bring back the laboratory component to the toxicology program, and did that. I also wanted to merge toxicology with risk assessment because the only reason to do toxicology is to address issues in risk assessment. To do that you have to work with regulatory agencies. So it became important for me to work with the EPA, to work with the FDA, to work with the Centers for Disease Control, Occupational Safety and Health Administration, say, "What is it that you need and can the toxicology program deliver?" It doesn't any good for us to just do our stovepipe vision with the toxicology test if it's not relevant to what regulatory agencies are doing, because that's why we do it. We do it as a public health activity -- the toxicologist program was formed out of the Public Health Service act in 1978, and I thought it was too tunnel-visioned in toxicology. So I wanted to bring in the basic scientists, bring in the policy makers and regulators and have them help us set up priorities. That's what I mean about being short-term. Out of that you can have long-term success in what the outcome of those deliberations were, and I also wanted to restore the feeling among NTP scientists, once I became director, to restore some of their sense of confidence that they were good, decent

first-class citizens within the National Institute of Environmental Health Scientists, because if people aren't feeling good about themselves, about what they're doing, they're not going to do it well.

SS: You were at the helm of the NTP during the height of the Human Genome Project. You were here during the development of the Environmental Genome Project, and also what became the National Center for Toxicogenomics. From your perspective, what are the implications of genomics for the National Toxicology Program?

GL: I think they're immense. I think there's tremendous opportunity, but we have to not just collect data. We have to ask questions. We have to say, "Can I identify an environmental estrogen, for example, by" and say, "What are the changes in gene expression from this?" That's just a collection of data exercise, and I've seen too much of it and it's really going to take us nowhere. We have to ask the fine questions: can I establish the relative potency among the class of chemicals based on gene expression data? Can I get a better handle of what the dose-response relationships are because I'm looking at a series of critical events? Can I make mathematical constructs to evaluate the relationship, functional relationship, between different genes? And all that gives me a system -- a sense of system's toxicology -- what are the sequence of events that are changed in toxic response, whether it be cancer or reproductive toxicity in that way address the issues of what are the sensitive subpopulations, based on either genetic predisposition or age or whatever. So the questions have to be really thought out, and if the question's a good one, genomics can supply the answer, if they're tractable. Some of the questions people would like to ask aren't tractable right now. For example, you're not going to be able to take a drop of your blood and my blood and say, "What have you been exposed to?" That's not going to happen for a long time.

SS: A really long time.

GL: We have to recognize that's not going to happen for a long time. There's too many difficult experimental variability questions that surround that issue. So as long as we are careful of how we ask our questions and not expect too much too soon…

SS: People really want what you just described -- some kind of molecular [unintelligible] analysis, and when I talk to them about these kinds of technologies what they fear are kind of the down-regulating of environmental chemicals, based on definitions of susceptible populations. Do you see that in our collective future in any significant way?

GL: I'm not quite sure what you asked --

SS: People are afraid that regulation will shift from population level, no one should be exposed to this substance at this level, to susceptibility groups specific regulation that says, "I know I'm sensitive to chemical acts, it then becomes my responsibility to make sure I don't get exposed," or whatever.

GL: Those are scientific as well as social questions. It's not only the -- there are workplace issues and then those sorts of things. We've dealt with them in different ways for a long time, like what do you do in terms of occupational protection for a woman who is pregnant?

SS: People who are susceptible to [unintelligible].

GL: We do make regulatory decisions on sensitive subpopulations, for example in the case of mercury. The safe exposure level based on personal consumption habits is based on consumption habits for women at childbearing age because mercury is a developmental neurotoxin. So we already do that to some extent. So I don't think it's a great leap to say we should do this because of genetic predisposition. The real difficult question comes in, how many people need to be sensitive before the government will step in to protect them? If there's one person in the world, then probably not. In the case of women at childbearing age -- there's an awful lot of women at childbearing age in this country, so the answer is clearly yes. So maybe 5% of the population -- yes, you protect them. But you also have to make it explicit that that's what your regulatory decision is based on. If it gets down to very low numbers, at some point you have to say, "No, we're not going to protect you." And where you draw that line is going to be the difficult question.

We do it now. We do it now at risk assessment. We do an occupational cancer assessment, and say, "Well, an acceptable cancer risk is 1 in 1000. If you're that 1 in 1000 it's not good for you, right? So that's what regulators do, they draw the line. So this would be no different. They just have a different line to draw, using a different set of tools and different kinds of information. So the answer is no, I'm not too worried about that. We always have been doing that and people who are responsible for those decisions just have to -- how many people will I protect?

SS: And now -- this is --

GL: And this has to be a public, open decision, because if it's not -- people have to understand what you're doing. You can't keep it under the rug. You'll say, "This decision is based on protecting this proportion of the population, and it's not based on protecting this group." People have to know that.

SS: We're off my interview schedule and just on to my personal interests.

GL: Right.

SS: Because -- especially about the mercury issue, because it seems like -- the advisories that have come out in the past month or so don't necessarily protect me as a woman of childbearing age, they tell me to protect myself, right, by monitoring my consumption of different sorts of fish

GL: What the Bush administration has done with mercury is a crime.

SS: Okay.

GL: I'm not uncertain about that.

SS: Okay, that's the kind of distinction I'm trying to think through. Do we regulate based on, say, 5% of the population being susceptible, or do we simply tell that 5% to change their behavior in some significant way? And what I hear you saying is that that's a risk assessment, risk management and a conundrum --

GL: That's right, because everyone agrees that fish is a good source of dietary protein.

SS: Right, I'm almost certainly about to go eat, so --

GL: And it's the same issues with breastfeeding, with dioxins -- breastfeeding is good for you, but breastfeeding would be better if there was less dioxin in breast milk. Eating fish would be better if there was less mercury in the fish. So you don't have to pick one or the other, you have to say, "So given that as a public health message, the best thing to do is get the dioxin out of the breast milk as best you can and get the mercury out of the fish as best you can, not to delay the regulations." Being over an acceptable level doesn't necessarily mean your baby's going to have a neurological problem; it only means you have a greater risk of that happening. Given that, the best thing to do is say, "How do we lower the body burdens of the people in this country, especially women of childbearing age, to [inaudible] mercury?" Not to do what's going on now. So that becomes the public health goal. If we do that then the risk will go down as well.

SS: Thank you for indulging my off-schedule questions. To return to the --

GL: I know a lot about the mercury thing because the White House asked me -- before I retired, I chaired the interagency group that was trying to come up with a common risk assessment for the Federal Agencies. I had to work with FDA, EPA, Oceanographic and Atmospheric Administration -- all the different agencies working with it who were at each other's throats over the mercury issue.

SS: And the consensus guidelines came out a couple of weeks ago. What did you think?

GL: We were partially successful.

SS: There is a consensus.

GL: Well we're going to range, we're going to range. We never [inaudible], which is maybe a success in itself, I don't know.

SS: I'm fascinated by this, but I'm also aware of the fact that you want to go. Is there anything we should have talked about that we didn't touch on?

GL: No, no.

SS: Okay, great.

GL: I think I told you everything I remember.

SS: Thank you.

End of Transcript