Shelby, Michael 2004

Dr. Michael Shelby Oral History 2004

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Dr. Mike Shelby Interview

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Interviewer: Dr. Sarah Shostak

Shostak: It's Monday, April 12th, and I'm interviewing Dr. Mike Shelby of the National Institute of Environmental Health Sciences (NIEHS). All right, so I've turned the tape deck on and you're aware that I'm taping, yes?

Mike Shelby: I'm aware, yes. I am being taped.

Shostak: So can we start by you telling me a bit about your educational background and your training in science?

MS: Well, I was interested in science from junior high or high school. I got a bachelor's degree in biology and chemistry from Central State College in Edmond, Oklahoma after attending Oklahoma State University for two and a half years. Following that, I worked about three years, including the last two years as a technician at Oak Ridge National Laboratory, in a Neurospora genetics lab there. Most of that time was spent on the biosatellite program. We were sending Neurospora spores into outer space and then recovering them after the satellites came down, assessing the radiation-induced mutations. Having come out of rural Oklahoma, education and science were kind of far-fetched at the time for me -- but I realized after a year or two at Oak Ridge that there were a lot of PhD's there and some of them were a lot smarter than me and some of them were not as smart as I was so, I figured I could get a PhD too.

Anyway, I started applying for grants to get into graduate school. I got a fellowship at the University of Tennessee, Knoxville, in the Department of Botany, interestingly enough, because they offered the best fellowship. But I continued working in Neurospora genetics, and I got my PhD there in '73. I went back and worked at Oak Ridge National Lab in something called the Environmental Mutagen Information Center. I started working there part-time while I was still in graduate school, and went back full-time when I graduated. I worked there for about four years and got tired of that work and contacted NIEHS because there had been a lot of people that had moved from Oak Ridge – the biology division there was slowly shrinking, and NIEHS was growing. EPA at RTP was also growing, so people were finding their way from east Tennessee, to RTP. So I got in touch with Fred de Serres, who was the Associate Director for Genetics at NIEHS. I had worked for him in Oak Ridge and he hired me over here at NIEHS. While working with Fred in the office of the Associate Director for Genetics Office, we ran three big international collaborative studies assessing the predictive value of short-term tests for chemical carcinogens. These studies were funded in large part by the WHO IPCS -- International Program for Chemical Safety. The books are there on the shelf. They all got published in book form, all three studies.

Then in about '80, '81 -- I can't remember -- the National Toxicology Program had come into existence. Ray Tennant had been hired out of Oak Ridge to come over here and head the CGTB – Cellular and Genetic Toxicology Branch -- and he was looking for people so I changed jobs within the institute went to work for Ray at that time. I built up the mammalian cytogenetics, and mammalian germ cell mutagenesis programs from scratch to a fairly large operation. It was all done by contract, so I was project officer on the studies looking at cytogenetic effects in human lymphocyte cultures. We had mouse bone marrow cytogenetic studies going on, and also built up a big germ cell mutagenesis program at Oak Ridge National Laboratory and began to look at the potential of chemicals to induce heritable changes in germ cells that lead to genetic disorders in subsequent generations.

I did that for several years. Some reorganizations occurred. I can't remember exactly what was happening at that point, but anyway I ended up working for Bern Schwetz, who was basically in the same position that Chris Portier has now, and George Lucier had before that. In this new position I started moving into reproductive and developmental toxicology. I did that for a few years, then some more reorganization occurred and I was made chief of the Laboratory of Toxicology, which I did for about 5 years or 6 years. During this time I set up the Center for Evaluation for Risks to Human Reproduction. I then volunteered that if they wanted to find a new branch chief, I would be happy to spend full time working on the Center. After a year or so they decided that was a good idea.

Shostak: How long has the Center existed?

MS: The Center was established in ’98. It took two or three years to get it to that point, but it came into existence in June ’98 so it’s 6 years old now. I’ve gone from genetic toxicology to reproductive and developmental toxicology and that’s where we are today.

Shostak: Okay, now of course I’m going to ask you a bunch of questions about everything you just told me.

MS: Right.

Shostak: When you were at Oak Ridge the first time, working on Neurospora genetics, whose lab was that?

MS: Dr. Fred de Serres.

Shostak: de Serres, who later came here.

MS: Right. He came here in ’72.

Shostak: Okay. And then when you went back and you were working with the Environmental Mutagen Information Center, who were your colleagues?

MS: John Wassom, Elizabeth Von Halle and Heinrich Malling, and in the beginning that was it. There were just four of us. As time went by we hired a few more people – Wilma Bernard, Beth Owens, Brad Whitfield and several others whose names I can’t remember.

Shostak: Is that project ongoing, and if so where is it located?

MS: No. NIEHS was always the primary funder for it. It was a database, a searchable database of the literature, where we collected the literature, indexed it, put it into computers and did searches, published bibliographies, that kind of thing. The institute here just decided it was no longer necessary, and I don’t know when that was -- that was maybe five years ago that they cut the funding for it, so I think it doesn’t exist any longer.

Shostak: Was it perceived as unnecessary because there’s a comparable resource?

MS: I think part of it was due to a kind of a declining interest in genetic toxicology. At that time, NIEHS had a branch dedicated to genetic toxicology.

Shostak: And that was –

MS: -- back in the early 80’s with Ray Tennant, and that no longer exists. There’s just not much action in that area any longer.

Shostak: From your perspective, why is there not much action in that area any longer?

MS: Well, I think the genetic toxicology sort of found it’s way into the fabric of toxicology, and the kinds of tests that were done, they way they were conducted, these things ….

[break in audio]

Shostak: It's back on, and if you could pick up on the topic of why environmental mutagenesis and genetic toxicology have developed around a focus on screening and testing for mutagenicity and carcinogenicity of chemicals.

MS: This goes back to the large number of chemicals that needed to be evaluated for their potential carcinogenicity, and that number is in the thousands, and the impossibility of doing that many tests in two-year rodent carcinogenicity studies; and not just because of the expense and the time required, but also because of our commitment to reducing, refining, replacing whole animal studies with other tests, where possible. So there were a large number of chemicals to be tested and there was a fairly sound mechanistic basis for using genetic tox tests to screen for carcinogens because there's a great deal of evidence that some, or many, or most chemical-induced tumors result from the DNA damage induced by those chemicals. So it was a practical reason and a scientific reason that these short-term tests held a great deal of promise. So that's why so much effort was put into them.

Then the reason there were so many tests being developed in addition to the Ames Salmonella test was that people thought that a bacterial cell could not reflect all the types of damage that might be induced in mammalian cells, which was the cell of concern. So, as I told you earlier, the easiest way to think of it is as a matrix witha variety of organisms down one axis - bacteria, eukaryotic microbes such as yeast, cultured mammalian cells, whole animals, rats or mice, and the study of genetic damage induced in them. The detection of gene mutations in cultured mammalian cells was very popular. There were several different assays that were available with that endpoint such as HPRT mutations in a variety of cells, the thymidine kinase locus and L5178Y cells.

So, there were a variety of organisms available to investigate these effects, and there were a variety of genetic endpoints that need to be looked at, from base pair substitutions to frame shift mutations, small deletions, chromosome aberrations, and aneuploidy or whole chromosome changes. A great deal of the activity over 15 or 20 years involved trying to figure out the best combinations of organisms and endpoints as genetic tox tests – which of those could best be combined to predict the potential carcinogenicity of a compound. So much of CGTB's activities –

Shostak: Cell genetics –

MS: -- Cellular and Genetic Toxicology Branch – went into that effort. In fact, we ended up publishing a paper in *Science,* which was kind of a culmination of our work in that area. And in the end we kind of dropped back to using the Ames tests and some measures of chromosome aberration damage in cultured cells, and in intact laboratory animals. I haven't worked in this area for five years or more in the institute. I think they're down to that; that they do Ames tests, some chromosome aberration tests in cultured Chinese hamster ovary cells, and *in vivo* they use a mouse bone marrow micronucleus or peripheral blood in micronucleus, which is a surrogate for standard metaphase analysis of chromosome aberrations. So, a lot of the action has diminished because they've just kind of settled on a few tests that they're going to use, and the tests never did prove to be as predictive as people had hoped they would be.

Shostak: Is that on their own or as compared to a two-year rodent bioassay?

MS: It's comparing genetic tox test results to the results of the two-year rodent bioassay. So, we just dropped back to two or three tests, and those were run fairly routinely on all the chemicals that come into the carcinogenesis bioassay program. So, all the hunting and searching and modifying protocols and looking for new organisms has kind of come to an end.

Shostak: It seems like the transgenic mouse models were part of this trajectory of looking for different sorts of bioassays. Could you help me understand their relationship to research that had been done in this area?

MS: Well, Ray Tennant is the best person to talk to you about those, or Ron Cannon or Jef French.

Shostak: I have talked to all three of them.

MS: You have?

Shostak: I have.

MS: Okay, then you've got more than I can tell you. I was never a great fan of the transgenics, but I understand how they work and the basis is theoretically good.

Shostak: May I ask you what kept you from being a fan?

MS: They seem oversimplified to me, that these are single gene changes in these two models that are most popular here at NIEHS. They did hold a promise of allowing one to screen for induced tumors in a shorter period of time with fewer animals, which was a big step forward, but it never set comfortably in my mind that these genetically-modified mice – specifically genetically modified in single gene – would be sufficiently predictive of what those chemicals would do in humans. It just seemed an oversimplification to me. I liked the fact that they were quick and less expensive. I didn't like the fact that they were based on these single transgenes.

Shostak: What are the full range of characteristics you look for in evaluating a bioassay?

MS: I don't evaluate bioassays, I haven't for years.

Shostak: What would you hope – what would a perfect tool do for you? "You" plural.

MS: Well, it would accurately predict those chemicals with the potential to cause cancer in humans, and they would do it quickly and inexpensively –

Shostak: with fewer animals….

MS: Right. The human population is so genetically diverse, and the animals that we use to study the induction of cancer are so genetically uniform that it's just difficult to know – to understand how they could be predictive of cancer induction in such a diverse population as the human population.

Shostak: Let me go back to a question about the history of genetic toxicology at the NIEHS. You've mentioned the Cellular and Genetic Toxicology Branch. Can you also just give me the names of the different labs or the different branches where this research was most significantly undertaken?

MS: Well as I mentioned earlier, the predecessor of the CGTB, whose name I can't remember is one. Heinrich Malling can tell you that because he was chief of it for some period of time. A lot of it went on in Carl Barrett's laboratory, the laboratory of carcinogenesis -- or the Laboratory of Molecular Carcinogenesis. I think those were probably the main places where this work went on.

Shostak: And then where did – part of what I'm trying to understand – I'll show you what I'm looking at – is how the laboratory of environmental carcinogenesis and mutagenesis was related to these others, and then my understanding is that this is basically the NTP. Right?

MS: Right.

Shostak: So just to get trying to understand how they work in this area was divided across these different labs.

MS: Well, it just kind of happened spontaneously. I'm not sure that there was any formal division of labor that went on. I mean, most of the intramural scientists have got a good deal of freedom in what they choose to investigate, so – this is a current?

Shostak: No, because – and the Laboratory of Environmental Carcinogenesis and Mutagenesis no longer exists, right? Tennant's with the National Center for Toxicogenomics. And Barrett, of course, is at NCI now. I interviewed him now, he was wonderful.

MS: Good. So, not much still goes on here. Most work now –

Shostak: In the Laboratory of Toxicology –

MS: -- right – is done by contract. Almost all of our testing is done – I guess all of our testing is done by contract. We just send the chemicals to the labs and they send us the test results back. There's no true focus inside NIEHS on this. You might want to talk to Kristine Witt who is the person that oversees all that now. She's remained deeply involved in it for many years, and she still is, and her memory's got more continuity in this than mine and she can fill you in on the details of what's happened since – whenever, '84 or something, when she came here.

Shostak: Okay, thank you. It's W-I-T-T?

MS: Mmm-hmm.

Shostak: Great. Again, a general question: when you were working in the area of genetic toxicology at the institute, how were resources allocated to those labs? Was there kind of a central plan for genetic toxicology or was it more independent investigator-initiated research?

MS: Again, that was Ray Tennant's business at the time. If I had projects that I wanted to downscale or upscale or change I went to Ray with the plan and he said yes or no, went a step higher and found out whether or not we had the resources to support it or not.

Shostak: Now Ray also came from Oak Ridge.

MS: Yes.

Shostak: But not from the Neurospora genetics --

MS: No, he was, I think, a viral oncologist.

Shostak: Were there ways in which those lines of research intersected?

MS: If there are, they're fairly vague. Ray's a very bright guy. He provides good leadership, he's got a lot of vision, he'd kind of flourish wherever he ends up, I think. He's a good promoter and salesman, so – I mean, they did not bring him here to head that branch because of his genetic toxicology experience, I don't think, but he did a very good job just the same, just based on general scientific knowledge and leadership skills.

Shostak: And how have the relationships between Oak Ridge and NIEHS been maintained over time?

MS: Well, we provided a lot of money to Oak Ridge. I can only speak for what I was involved in. At that time, 20 years ago, Julian Preston was still at Oak Ridge, a world class human cytogeneticist; and did a lot of human cytogenetic studies for the program. Bill and Lee Russell, Waldy Generoso and that group in Mammalian Genetics Program over there were a primary source of studies on germ cell mutagenesis. So we put a lot of money into Oak Ridge for several years on both of those programs. I had an e-mail recently from John Wassom saying that they were closing the last building of the biology division at Oak Ridge, so it no longer exists as such. They've got a new mammalian genetics facility over at the X10 plant. The old Biology Division was located at the Y12 facility. So it seems that it's just petered out completely, except for the mammalian mutagenesis studies. But there was a considerable amount of interaction, funding, visits, seminars back and forth between the two places.

Shostak: One of the things that I've noticed in my reading is that the focus on genetics at Oak Ridge seemed to be on the damage to human genetic material caused by exogenous agents, whereas the focus at NIEHS seems to be both that and also questions of genetic susceptibility, genetic diversity. Has that been a shift that you've observed over time or were those two genetic foci always present?

MS: I think the latter one that you mentioned, of variability and susceptible subpopulations; is newer than the old concern, about simply the effects of chemicals on genetic material. As understanding of human genetics and DNA repair processes and other genes that determine metabolism, all of these various genes that can impact susceptibility -- as an understanding of those has grown, then so has this second area that you're talking about. It suggests a natural progression, I think, rather than any kind of a shift.

Shostak: And one doesn't exclude the other in any way, correct?

MS: No. Absolutely.

Shostak: They can both be investigated together. And – how do I want to ask this – does susceptibility have a role in the testing and screening of genetic toxicology now?

MS: At the moment I can't see how it has a role in the screening. It seems to me to be a step further down the line, that once you can -- through screening -- determine the kinds of genetic damage that may be induced by an environmental agent and have some understanding of the mechanisms by which that occurs then you can gain an appreciation

for what variables, what genetic variables might reduce or increase the susceptibility to that damage. So I wouldn't consider it a part of the screening -- not of the chemical screening, maybe of the human screening to know what people's genetic makeup is. That might provide information on what chemicals certain subgroups might particularly want to avoid or be protected from.

Shostak: Okay that's helpful, thank you. If you were to describe the current state of genetic toxicology, how would you describe it?

MS: I'm not in a very good position to – since I don't currently work in genetic tox, after 25 years as an insider, I have to look at it as in outsider now. That'll take some thought. I suppose that what we were just talking about; is one of the areas that may be most active in the area of genetic tox now - genetic variability, and the variation in susceptibility to genetic damage and how it's expressed as genetic disease -- whether it's a somatic disease such as cancer or a heritable disorder due to genetic damage to sperm or eggs. A lot of the emphasis in the Environmental Mutagen Society is on DNA repair, which is not a new field by any means but one that is much more strongly represented within the Environmental Mutagen Society, the agenda of our annual meetings, and the papers that appear in the journal.

Shostak: Do you still go to the EMS meetings?

MS: I do.

Shostak: Have they changed significantly over time? In what way?

MS: Yeah, very much so, just along the lines we've been talking about. When I first went in '74 it was all about testing. And back then the assays were different. There was a period of time when a host-mediated assay was popular and then Drosophila was much more widely used in testing and screening. Those areas are now of little interest in the screening field. There was this big period of new assay development in the studies to try to determine the predictive values of the individual assays and the assays in various combinations, which lasted years and years, and now there are other interests. The whole genomics phenomenon, the ability to sequence DNA, mini-satellite, micro-satellite mutations are a big issue. Within the EMS, DNA repair is the topic of growing interest and substantial activity. So it has changed a lot.

Shostak: This is a somewhat different topic, but in what ways, if any, is toxicogenomics related to the research in general that began in the EMS? Is there a relationship there, is probably the first question.

MS: Well, if you could define what you mean by toxicogenomics it might be easier, but in my mind it's increases or decreases in transcription of specific genes that follow exposure to some external agent. And in that sense, it's not very closely -- in my mind -- related to genetic tox.

Shostak: The focus was on genetic damage?

MS: Right, the DNA, and this is expression of the genes. Those changes by no means require a change in the DNA. So it's the expression machinery that's important there. So although there might be a relationship that I don't see, I'm not aware of it.

Shostak: And again, another question about differentiating areas of science: in what ways are genetic toxicology and environmental carcinogenesis similar or different emphases of study within the environmental health sciences?

MS: Well, I believe they are still very closely related and have been since the onset of the environmental mutagenesis field because a major public health concern is cancer. I don't keep up with the literature anymore, but you still see papers coming out on the kinds of genetic damage that's found in specific genes. In oncogenes or tumor suppressor genes in tumor tissues of humans and animals, and that's all related to the kinds of damage -- genetic damage, DNA damage -- that was induced and possibly led to the initiation of those tumors. That's the very thing the genetic tox people look at. Whereas the genetic tox people are characterizing the genetic effects of the chemical, cancer people are technically characterizing the kinds of genetic damage that occurs in tumors, or pre-tumor tissue, without knowing what the chemical is they were exposed to. So there again, it's a continuum, I think, of scientific events that are closely related, and perhaps causally related in many situations.

Shostak: Just a couple more questions – what are the biggest changes in science that you have observed over the course of your career?

MS: The biggest change in science in the course --

Shostak: Or the most significant.

MS: Is probably the financial changes that have occurred.

Shostak: What do you mean?

MS: I mean patents and intellectual property and the fortunes that have been made on it, which was virtually unheard of when I first got into science. Nobody even thought of it. I think it's probably funding, the way the funding is – the difficulty of obtaining funding is probably greater than it was 20 or 25 years ago. There are more scientists around and even though the pie is bigger, the number of people wanting a piece of that pie has also greatly increased.

Shostak: What other changes or developments that have been most significant to your work as a scientist?

MS: Well, clearly it's the molecular biology, the capability and the technology to move down closer and closer to the primary events that cause changes in biological systems. I'm not that old, but it was pretty crude in 1970 compared to what we can do just 34 years later. And that trend continues, I think. The technology that just allows us to look at smaller and smaller and smaller units, and by doing that gain greater appreciation for the mechanisms by which toxic effects occur, and that being hardly any different from understanding how biology works, because – you're perturbing processes and molecules and structures that have to be intact, and in order not to get toxic effects you've got to understand the basic biology before you can understand the toxicology, by understanding what you're disrupting. So those are three big changes.

Shostak: Anything I should have asked you that I've not yet asked you? About the history of the Institute, the history of genetic toxicology, changes in the environmental health sciences?

MS: No, I don't think so. If there are, you'll think of –

Shostak: Later…

MS: You'll be back on the email. Yes.

Shostak: Let me ask, are there ways in which your career in environmental health science has been significantly similar or significantly different than what you imagined when you went off do get that PhD?

MS: I didn't have an idea of where I was going then. There are people that have much better plans than I do. I'm just a victim of winds of fate. I watch for opportunities, I try to make sure that what I do is done well. The reason that I'm where I am now instead of back in the laboratory of toxicology is that I had reached a stage in my life where I felt like I needed to do something that had a more immediate health impact than overseeing six or seven research groups and taking care of budgets and personnel problems and organizational business. The Center here has allowed me to do that, and I have to say, it's gratifying. I don't have many resources, human or otherwise, to oversee but I've got enough to do the job that we set out to do. I was never a basic researcher at heart or in practice, but I was always concerned with public health issues, and the CERHR allows me to – in the twilight of my career – do something that I can see the impact of, rather than saying, "Oh we'll do this, and somewhere down the line it'll be useful to the people out there. Somebody will pick it up and do something with it." So I'm happy in what I'm doing now.

Shostak: Which is great.

MS: It's good, you bet.

Shostak: What are the major projects that the CERHR are working on right now?

MS: Well, we're just putting the final touches on the expert panel report on fluoxetine hydrochloride -- you may know as Prozac -- and its possible impact on reproduction and development in humans. A month from now we've got an expert panel convening to do the same kind of evaluation on acrylamide, which is recently in the news because it's found in french fries.

Shostak: Right. All sorts of fried foods, right?

MS: Right, yeah. Especially starchy foods cooked at high temperatures. And it's already known as a rodent carcinogen, it's a neurotoxic in humans and rodents, it's a germ cell mutagen in rodents. So, it's a bad actor but the amounts of acrylamide in the diet are, by some measures, very, very small. I think that the challenge of the acrylamide expert panel is going to be more one of drawing a conclusion about whether or not the levels we're exposed to, as best we understand them, pose a risk or not.

Shostak: What would the risk reduction for acrylamide be? Don't eat french fries? Already, I can't eat tuna?

MS: You have to forget all those wonderful dinners you had of french fries and tuna. I mean, I don't know. The food industry, I know, is already working on it, putting things in or taking things out or changing the cooking process to reduce acrylamide levels. In fact, it's not even clear that it's a risk at this point. It's got enough press -- in fact it was on the news this morning before I came in. But it becomes a dose issue now. Maybe the doses are low enough that it's not causing any harm, we don't yet know. So anyway, those are the kinds of things we're doing.

End of transcript