

Dr. Anne Sassaman Interview

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Sara Shostak: It's Monday, April 12<sup>th</sup> and I'm interviewing Dr. Anne Sassaman of the National Institute of Environmental Health Sciences.

SS: So you're aware that I'm taping our conversation? ... I'll put that there. I'd like us to start just—would you tell me a bit about your education and your training and how you came to NIEHS?

AS: OK. My background is with a bachelor's in chemistry and Ph.D. in microbiology immunology really focusing on immunochemistry from Duke. My undergraduate was at Auburn. And then I did a post-doc in biochemistry at Duke. I went to Bethesda to actually enter Federal service in the what was at that time the Bureau of Biologics at FDA which had been a part of NIH. It was on the NIH campus, and I did research there for two years before going to the Heart, Lung and Blood Institute, where I was then working as an extramural staffer in the Blood Diseases Branch. Actually I was doing research administration in the same area that I had been doing research in. I became chief of that branch. I was there at the NHLBI for, I guess, 10 years, and then had an opportunity to come here. I was able to expand my responsibilities beyond just the program area to be responsible for all of the extramural activities here at this institute because it's, by virtue of being a smaller institute, we have everything consolidated in one division. So that's basically how I got here and I've been here longer than I can believe.

SS: You came here in 1986?

AS: Yes.

SS: What were the focal areas of the DERT when you arrived?

AS: Well, I guess the mission of this institute has always been very broad and it—probably the focus was still, at that point, primarily on chemicals. The National Toxicology Program was relatively young, I'd say, and it evolved from the Cancer Bioassay Program so that it was still sort of the main thing of testing chemicals. A significant interest in cancer as an endpoint, but the extramural program at that point was very undirected. They had not had—I think they had had maybe one request for applications to target research but that was about it. So, we've changed an awful lot since then.

SS: Can you tell me about those changes?

AS: Yes. Certainly one of the major changes has been with Dr. Olden's leadership in really moving from a program that was primarily toxicology, primarily focused on chemicals, to a more public health oriented focus. Looking at non-cancer endpoints and really expanding the definition of the environment much, much beyond chemicals so that that's given us a very different audience, a very different clientele for our efforts and our portfolio. So, the challenge has really been in managing this expanded definition of environment, and essentially an

expansion of our portfolio, with still a very relatively modest budget in which to do all of these things.

So we've had a real growth in the number of solicited programs, targeted activities, and that's been necessary to make these changes in direction and so forth. Now about a third of our portfolio, our research project grant portfolio, is in targeted programs. So, that's been a major, major change and, of course, that means a lot of changes in terms of the staff that are required to manage these programs and their responsibilities and so forth. It's not just having relatively simple R01 type grants to manage but consortia and Centers' programs and that sort of thing. So, it's much more—a much higher level of engagement with the scientific community in getting these things done—so, much more complex.

SS: You mentioned an expansion of the definition of environment.

AS: Yes

SS: Can you help me understand what the initial and then the expanded definitions have been?

AS: Well, as I said, in general the initial definition, or the primary focus, was on chemicals—man-made chemicals and the chemical industry and that sort of thing. Now we are looking at—for example, probably the most drastic change is the looking at the social environment and how social environment and physical environment interact, in particular in determining susceptibility to disease and the exposures that one might encounter and lifestyle factors and that sort of thing. So, we have—actually I have a slide that lists all of the things that we include in the environment which is not only byproducts of industrial activities or chemicals but physical factors such as electromagnetic fields, for example. Then, we include pharmaceuticals if they can be considered an exposure. The social factors, we are now looking at the built environment and just a whole range of things that were not even considered 15 years ago.

SS: What accounts for that shift in definition?

AS: Well, I think it's—part of it is a growing recognition that we encounter all of these things in our daily lives and that not only is there a much broader range of environmental factors but that these are not encountered singly but in combination and so that also really increases the complexity of what we're doing. We're just beginning to scratch the surface of trying to devise ways to look at mixtures of chemicals much less mixtures, if you will, of these different factors—of social and behavioral factors, environmental, that sort of thing.

SS: I know that in the time, let's say from 1986 until the present, NIEHS has undergone at least one significant reorganization. Since you've arrived what consequences, if any, have reorganizations had on the DERT?

AS: Well, one reorganization that occurred, maybe about 10 or 11 years ago, resulted in the Research Contracts Branch being made part of the extramural division. We had—shortly after that we had an internal reorganization that created two different parts of this division which turned out not to be the most effective way of running the division, so we sort of went back to an older model of a single division, actually, about a year ago. But probably the big reorganization of having an intramural division and an extramural division has not affected what we do so much here as it has other parts of the institute.

SS: OK. And also, just as part of my effort to understand the relationships between the different pieces of the institute, in what ways, if any, are their research agendas of the DIR, the DERT and then the NTP in relation to each other?

AS: Well, first of all, the NTP is part of DIR.

SS: Right.

AS: Yes, you understand that? So it's not a separate organizational entity here, but I would say that there is a reasonable effort to at least coordinate, not duplicate, activities. The intramural laboratories and the principle investigators there are much more able to do basic research that, perhaps, has a little lower degree of mission relevance. Either they are continually challenged and, I think, particularly right now, to make the case that whatever they are doing is relevant to environmental health sciences, but in many cases the work that's being done in some of these laboratories, if it was submitted through the extramural group would not be assigned to this institute because it's more basic fundamental biology of systems rather than looking directly at the environmental impact.

That being said, I think that probably more than most institutes, having been in a different institute and a larger institute and working in Bethesda on the campus for a number of years and having recruited people here from a variety of other institutes, that we have more communication and collaboration between our extramural staff and our intramural staff than most institutes—than occurs at most institutes. And I think that's healthy.

SS: How has that been possible?

AS: I think that a lot of it has to do with the size of the institute, the fact that we're all here together. Even though we have never physically been located on the main campus, and when the main campus was the old campus which you passed on Alexander Drive on your way between here and...

SS: Right.

AS: At the time I came here the extramural division was on that campus and there were still some intramural labs there, and it was a setting where it was very conducive to seeing people, having lunch at the same picnic tables, that sort of thing. But, even though now we are separated by a couple of miles from Alexander Drive, still there's much more physical interaction. More opportunity for interaction than I think on the Bethesda campus. Because now, particularly, but even over the years the extramural activities, components, of most institutes are off campus and what I have learned is that sometimes their physical separation from the main campus, that the result of that in terms of communication is not that much different between being here and being there. We are all using electronic communication and that with parking and shuttle schedules and everything else people do not interact that much face-to-face. But we have many more opportunities here to do that, so I think that's part of it.

SS: Because the Comparative Mouse Genomics Center Consortium is part—or, is related to the Environmental Genome Project, could you describe the development of the Environmental Genome Project for me?

AS: I'm kind of going back in my memory bank!

SS: To about the mid-90s.

AS: Yes. And I—well, we were obviously aware of what was going on in the Human Genome Project and the advances that were being made, particularly in the technology. I do remember when we started thinking about this wondering how we were going to get the resources that looked like it was going to be necessary—monetary resources—because everything seemed to be so expensive at that time and the estimate—I don't remember what the numbers were, but they were pretty high. When we started looking at thinking about how we should be taking advantage of information that was coming from the Human Genome Project and recognizing that this triangle that we had developed of “exposure, susceptibility and age”, which I'm sure you've seen, that that susceptibility component was going to be largely a genetic component. We kind of realized that seeing that there are a lot of things that go into susceptibility that go into susceptibility that are not simply genetic, but—

SS: Such as socio-cultural components?

AS: Yeah, right. But that we really were going to need to make a focused effort to see what this genetic susceptibility would be like. So, that was really the given of the Environmental Genome Project. To look, to identify—or at least begin identifying those what we call environmentally relevant genes and to focus on those in terms of looking at, as one of the first projects, the resequencing. Then looking at SNPs and then, as the technology was developing and the cost was going down, we were able to look at it in terms of broadening—in the beginning we had sort of a staged plan of how we could take the information and then apply it in different

ways. There actually is a very nice poster that is in our conference room down the hall which I'd like to show you when we're finished that sort of maps this all out.

So after we got the resequencing started and looking at SNPs, we realized that eventually we were going to want to look at these in human populations, so we developed a program of planning grants for epidemiology to allow people to start thinking about how they would go about using this, and so forth, as part of the next step. And then that was when we realized that all of these could benefit by developing the animal models. When the concept of taking what we knew about these environmentally relevant genes in humans and developing mouse models of those polymorphisms and seeing how those could be used to get to this ultimate goal of learning what makes people susceptible and not susceptible to these exposures. So that was kind of the approach and the reason for looking at models as being a significant step along the way. Now that we've got these SNPs, and I don't recall the exact number but it's a very large number, the picture gets more complicated.

SS: In what way?

AS: Well, recognizing that one SNP alone is probably not going to be an answer so now we're looking at haplotypes. And we have to devise ways of looking at the phenotype, looking at the functionality of these SNPs, and so out of these hundreds, what really is going to make a difference. How are you going to approach this so that it is not sort of a shotgun approach? Or, as I have been asking myself, because I'm not a geneticist, I'm not a mouse person. A lot of this is not something that I have a lot of in-depth knowledge about, so my question is how do you take all of this and make a rational approach so that you're not just bound by the sheer luck of finding which one or which combinations. I think that's one of the big challenges right now.

SS: So the Comparative Mouse Genomics Consortium was initiated as part of the Environmental Genome Project.

AS: Right.

SS: You've already spoken to this a little bit, let me go ahead and ask the ways in which the consortium is integrated within the genome project – the Environmental Genome Project.

AS: Well, we have – because we have all these various parts. We have an internal working group of the various scientist administrators who are responsible for these different parts and they meet on a fairly regular basis. They have held joint meetings of the extramural investigators who are working on these various parts to try to keep the sense of integration of all of these parts so that they're not

- viewed as stand alone pieces but part of a bigger plan, a bigger picture, of where the institute is trying to go.
- SS: And in what ways do the centers participating in the consortium serve the research needs of the Environmental Genome Project?
- AS: Well, they have developed a number of models. As I said, the challenge now is sort of doing the phenotyping to know which ones may be valuable. We are in the process now of doing the next step, as far as the center's program is concerned, and that is negotiating to put these strains into a repository so that then they will be available to the larger extramural community. We recognize that these, I think it's four centers, are not the only places with an interest or the capabilities for this and that this really from the beginning was intended to be a resource. This part, these centers would do the developmental part and then making the models available to the community through the repository would then allow us to have a multiplier effect in terms of the information that could be gained from.
- SS: And just to make sure that I'm following, these would be models of different sorts of susceptibility to environmental exposures?
- AS: That's the idea.
- SS: Okay.
- AS: I think it's pretty complicated. I think it's a big challenge.
- SS: Again I realize that you've spoken to this but what constitutes those challenges?
- AS: Well, just knowing what it really means and whether this SNP – how it may be related to another or how it fits into a pathway so that we can really get a handle on what it is that is causing the differences in susceptibility. Again, not being a geneticist, I had my own sort of conception of how complicated this is and in our discussions internally and so forth it does seem to be a big challenge to see how and perhaps our initial thinking of a SNP in relation to one SNP to a phenotype was simplistic.
- SS: You also mentioned that over the past years since you've come to understand susceptibility as a multifactorial phenomenon for those with genetic susceptibility and then sorts of socio-cultural susceptibility. Is there any role for these transgenic models for studying kinds of susceptibility other than genetic susceptibility?
- AS: I think there may be a lot of things that come out of this that are unexpected. One of the things that has come out of this program is almost, and I don't know a lot of details about this, but one of the models that had not shown any particular interest

in the mice at a young age, maybe even middle age, whatever age middle age is for a mouse.

SS: I think about a year.

AS: But as these mice aged the investigators noticed that they had a tendency to develop diabetes. So there seems to be maybe some impact of aging on this particular – with this particular polymorphism. That is not something that we would have been looking for and that's why I say that I think that we maybe surprised at what people are going to learn in this that may be unrelated to our initial goals of looking at susceptibility to an environmental agent and maybe aging is the susceptibility factor.

SS: Interesting. Are there a set number of endpoints that are being focused on by the Centers Consortium?

AS: Well, we are looking now at only two classes of the environmentally relevant genes and I think there are five categories. That was a decision that was made primarily on the basis of resources. So they're focusing on those categories of genes that in terms of endpoints susceptibility to what disease or dysfunction that is not a...

SS: And the Environmental Genome Project includes cancer and non-cancer endpoints?

AS: Yes.

SS: Correct? Okay.

AS: And so a number of these models now are looking like they're – that cancer is the endpoint.

SS: Okay. So, backing up a bit were there any particular scientific or technological innovations that made the development of the Centers Consortium possible?

AS: I'm not familiar enough with the details to really be able to answer that. I think that some things have come out of it in terms of the technology, in terms of the databases and so forth, that have really perhaps gone beyond our initial expectations, but I can't tell you – I'm not familiar enough with the technology to know – to be able to answer that.

SS: Could you tell me how the Consortium was put together, how it emerged?

AS: It was through a competition, peer-reviewed. So, it was – the solicitation was written in such a way that these people knew that they were going to collaborate

and cooperate and the initial program person – I don't know if you had a chance to talk with Jose Velazquez.

SS: Not yet.

AS: Okay, because Jose can really tell you a lot about that even more so than Joan Packerham who came into the program a little bit later working as a more junior person with Jose. Jose did a lot of work to get these people to work together. They are very strong investigators, there are some very strong personalities and getting people to agree on how you are going to do this in a consortium, everything takes quite a bit of negotiation. But the idea all along was that they would be – they were chosen to have a variety of approaches and a variety of targets, if you will, so we didn't have everybody working on the same thing. So, the responsibility of the institute staff has been to put all of that together into a coherent program.

SS: What sorts of translation does the Center Consortium envision or aspire to?

AS: Translation being taking it from the models to whatever?

SS: Mmm, hmm.

AS: I actually couldn't tell you what they individually would hope to that. I think as the institute and the program is concerned that this repository is a major activity in terms of translation because of just providing this resource and making it available and then having a much greater impact by having it available and hopefully a number of laboratories use it. And then, of course, there is the translation beyond that but this particular resource I think that – or activity I think the resource itself is sort of a translational one.

SS: Okay. That's very helpful. What, so far, has been the response of the extramural community to the Center Consortium and to the conceptualization of this repository?

AS: I think that the investigators are leaders in the field so that through their normal interactions they've been able to give some visibility to this program. I think we're just now reaching the stage where we're going to see the reception, because we've got to get this repository. It will be through the National Center for Research Resources and we're in the final stages of developing our memorandum of understanding and providing the funding for these to go into that repository. So, the repository has not actually been established yet, so it's a little premature in that regard.

SS: Have there been other significant DERT programs focused on model development?

AS: We have had some activities looking at alternative models for toxicology testing which has been, I would say, modestly successful – trying to get away from mice and rats and particularly no mammalian models in response to a lot of the concerns of reducing the number of animals used in research. That's been very difficult so that's where we've had some targeted efforts to develop transgenics early on in the transgenic arena.

SS: Can you tell me a bit more about this?

AS: Not without doing some back – more than just in my brain [laugh].

SS: Okay. Has the DERT initiative in the area of transgenics had any association with, or relation to, the DIR research on transgenics as carcinogen bioassays?

AS: We have a lot of conversation about that and certainly at an intellectual level and people talking with each other, knowing what's happening and being aware of it, but I'm not sure that there's been a lot of – because that has been primarily focused on models for testing. Other than our looking at alternative models, which, were not transgenic rodents, probably not too much.

SS: And is that because the DERT in general isn't focused on prediction and testing?

AS: It's not a major focus.

SS: Okay.

AS: And we'd probably be, if I had to describe it, looking more at models to understand mechanisms than models for testing.

SS: Okay, and has that been a focus of DERT during your entire tenure here, has that been an emerging focus?

AS: I think we have gotten much more focused on looking at mechanisms as a way of then being able to predict and to expand the biology as opposed to just looking at an endpoint and testing – if that makes sense.

SS: I think so.

AS: Okay.

SS: I noticed when I was on the south campus in the hallway there's a picture of Dr. Olden and Dr. Wilson and yourself and Dr. Birnbaumer and the descriptions of the programs under each director and, at the time that sign was made, it seemed that the programs were organized differently.

AS: Yeah, I haven't looked at that in a long time.

SS: Than they are now...

AS: What's it look like?

SS: Well, what caught my eye in particular, and this is a more current, from your website, that the picture in the hallway there is a program focused specifically on cancer which seems not to have it's own program in this organizational chart and I'm just wondering where research on carcinogenesis is located now or if it's distributed across.

AS: Well, it's distributed.

SS: Okay.

AS: And it's probably mainly in the Susceptibility and Population Health Branch that would be where most of it is. We're in the process of examining our portfolio and the distribution among these three program branches, but what we find is that there's so much overlap. That this has been one of the challenges as long as I've been here. Particularly when we started – well when I first came there was only one program branch and one review branch and one grants management branch, but when we started trying to divide up the portfolio as we became – as we grew. Do you divide according to endpoint? Do you divide according to exposure of the chemical or whatever the exposure is? There's no way of drawing chalk lines, so things tended to be integrated in all of the programs, but most of the carcinogenesis would be in Susceptibility and Population.

SS: Okay, and a related question. I've been tracking the development of research on mutagenesis in the DIR. Has there been a strong tradition of research on mutagenesis in the DERT as well?

AS: I don't know if I would say it's strong, but it's been a part.

SS: And similarly distributed across different programs,

AS: But probably mostly in this branch.

SS: In Susceptibility?

AS: Yeah. We changed the names of these three components about a year ago and just coming up with the new names was a real challenge. We kind of had a little contest about that, but you've made me real curious now on what's on that picture and poster. I'm going to go look...just walk past it.

SS: I think there are four or five sub-programs, but because my project is focused on carcinogenesis I needed the carcinogenesis and it was the cancer program that really caught my eye.

AS: I'll take a look at that.

SS: Let me get back to this. This is a totally speculative question, but because you mentioned that you were working in the Center for Biologics that was part of the NIH. Then it became part of the FDA, one of the things that we've discussed in my office, because one of my colleagues is writing a history of the intramural program, are the efforts to try to demarcate research that's done primarily for clinical applications from research that's done primarily for regulatory applications. This has been interesting to me because the NIEHS clearly does both, and I wonder if you could talk to me a bit about the consequences of having that sort of dual focus represented in the portfolio that the DERT manages?

AS: Well, I think that we really tried to make it clear that we are research focused. I would say that our conversations about this are related to overlapping interest between our program and part of EPA and we have some joint programs and we see there the real tension in a regulatory agency between the regulatory mandates and the priority of that versus the basic research. So, I'm not sure if I'm answering your question or not.

SS: You are, but could you tell me more about what that tension is?

AS: Well, what it means is that when resources get tight that the regulatory responsibilities are the highest priority. So, what we see is increased pressure on the research part and when we're funding something jointly then we really have had some concerns about whether EPA is going to be able to continue to meet their commitments. The scientific community, we've found, has been burned so many times by having instituted a program with funding from EPA and then having it cut off because the funds weren't there, because of the priorities being elsewhere. So that is a real example of the tensions in terms of resources.

Now, the other tension was in terms of what you do with the findings. And we are lucky because we can decide this is what the research show. We fund this research to be in support of good science to make these good regulatory decisions. We don't have to claim any responsibility for going one way or the other, but I think that there is increasing concern that the science that's used for regulation may be coming under greater scrutiny. The Shelby Amendment and some of the things that have occurred in the last few years, having investigators release data – raw data that they normally would not have under a grant or assistance mechanism. Some of those blurring of the lines is occurring.

SS: One of the rationales for the Environmental Genome Project and then, I assume by extension for the Comparative Mouse Genomics Center Consortium, is that it

could improve the scientific basis for risk assessment and for policy making. Are there any examples of that happening to date, so inclusion of information on genetic variability in risk assessment and regulation?

AS: I can make a suggestion of who you should talk to.

SS: Great.

AS: And that would probably be Ray [Tennant] about the efforts that are being made and this more in the toxico-genomics part, but in using genomic data, expression data and some of the things that are going on in FDA, I believe, is a little bit ahead of EPA in this.

SS: They always are.

AS: How to begin to incorporate some of that, or at least explore how it could be incorporated, without jeopardizing the companies; or whatever that are trying to get a product because we don't know what it all means at this point. Nevertheless being a bit forward thinking of how you can do it and how they can begin to be getting some experience and collecting some information that will help them know how best to use it.

SS: Just two more questions. One of the things that fascinates me about the DERT and the institute in general, is that it's been moving simultaneously to the molecular level and to the social level.

AS: Yeah.

SS: And that's an incredible breadth for a scientific program to try to envelop. How do you think about making the creation of such a multilevel and varied research agenda?

AS: It's kind of schizophrenic and we have internal discussions about this. I rely a lot on the staff and putting a priority on our internal communications so that we don't get polarized. We look for ways of bringing these two extremes together, at least in an informative way, as opposed to staying at these opposite ends. But you're right, it is an incredible range and when I talk about the breadth of the mission you can look at that breadth in all sorts of ways, but certainly the approaches of whether you're looking at the sort of macro-social. And as we get into this built environmental thing that's even well going even further away from the molecular level, but on the other hand this whole growing interest in systems biology is beginning to sort of put things in a bigger picture even the molecular things. So...

SS: Will, you help me to understand that? I'm still trying to wrap my brain around...

- AS: In years past it's been described as physiology, you know. It's looking at pathways and it's looking at how things relate to each other at an organ or systems or an organism level as opposed to at just the molecular level.
- SS: And then it could include the way the organisms function in different social or built environments?
- AS: Well, I think that's next generation systems biology. But I think if you think of it in terms of again – my husband was a biologist and he's never been involved in research, and he's very much sort of an integrative type of approach to things and when I started talking to him about it he was the first one to say to me, "Oh, this is just physiology." So, I think if you think of it in those terms that maybe the easiest way of understanding what it is.
- SS: Okay that's very helpful. And then my last question, which I ask everyone, is what should I have asked you that I missed?
- AS: I'm not sure I can think of anything at this point. There have been so many challenges over the last 18 years and there's been so many changes that sometimes I look back and am amazed at seeing how far we've come and it doesn't seem like it's been that long.
- SS: Okay what sorts of changes have surprised you the most.
- AS: Probably the whole expansion into these – what I don't mean to be using a demeaning term when I talk about softer science areas and how successful we've been at that. I remember when we first started talking about doing some work in health disparities and looking at the interaction of all of these social and environmental factors; having to really fight the battle at NIH. We actually had to have Wendy Baldwin who was the Deputy Director for Extramural Research intervene and call everybody together in her office to keep some of the other institutes that had longer standing programs in social and behavioral sciences, to keep from blocking us from starting these. "You don't have any behavioral science – you don't have any sociology – what do you know about that?" Just fighting those battles to get some degree of creditability for our interest. Since then we have hired a social scientist and we do have that expertise and these programs have been successful and we've been able to form some collaborations that I think some of the more traditional behavioral social science programs in other institutes, which I will not name, have not been able to do.
- SS: It's interesting for me to hear you say that because I have a colleague who is a sociologist who studies environmental breast cancer activism. She sent me an email a couple of months ago that said, "I know you work on the history of NIEHS and this is what I want to know, why do all of my activists want them to get money? What is it that's different between NIEHS and NCI?" And I don't have the answer to that question, but I think part of it lies in what you're talking

about right now that there have been some partnerships made – that there is a perception that the NIEHS is responsive to community concern.

AS: Right. Well, I think part of it is the size of the organization. I mean, NCI is huge. And if you were an outside person what you would have to go through in terms of the organization and the bureaucracy stuff up there to be heard. Ken Olden is extremely responsive to individuals and organizations. I think he really believes in this concept of we are here to listen and to be responsive in a responsible way, not to promise things we can't do. But to hear what people are concerned about and to help educate people about things where the environment isn't a major factor and then to really put some effort into exploring those diseases, and that's another things about the public health focus and the disease focus that we had not had in years past.

SS: A related question, I've done a number of interviews with environmental justice activists over the years and many of them are simultaneously very supportive of the institute's initiatives in environmental justice and very concerned about the implications of genomics for environmental justice. I'm wondering if that's come across your desk and if so what your response to it has been.

AS: Well, we have actually a solicitation looking at the ELSI [Ethical, Legal, and Social Implications] impacts of what we are – of our programs and are very much aware of these concerns and the importance of looking – not waiting until it's too late to begin to address these things so our staff person who is the social scientist, Shoba...

SS: Shoba.

AS: Yeah, do you know Shoba?

SS: I was an intern here three summers ago two summers ago, and she spoke to the group of interns when I was here.

AS: Well you might want to talk to her again.

SS: Anything else?

AS: I can't think of anything else.

AS: All right, then I will turn this off.

*End of transcript*