Dr. Frank Johnson
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Sara Shostak: You're aware of the fact that I'm taping our conversation.

Frank Johnson: I'm aware of the fact.

Shostak: Great. And it's barely picking you up, so I'll move it a little closer.

Johnson: Okay, that's fine.

Shostak: So, in terms of where to start, my sense is that you're one of the folks who could help me understand a bit about the history of the NIEHS and the National Toxicology Program. When did you first arrived here?

Johnson: Seventy-seven, 1977. And I don't believe I'm officially a part of the NTP. However, some of the work that I've done relates to the NTP and the mission of NTP. My formal title is research geneticist, and I came here to set up a laboratory operation, basically, and that operation had to do with detecting mutations in mice. The relevance to that is that there is, there seems to be a lot of overlap between compounds that are mutagenic and compounds that are carcinogenic, and carcinogenicity and identifying carcinogens is a big part of the mission of NTP. So that's how I fit in, I guess.

Shostak: So you arrived here in 1977 as a part of which laboratory?

Johnson: The Laboratory of Genetics.

Shostak: Okay. And can you detail for me how you've moved through the institute since that time?

Johnson: Well, I forget dates, things like that, but the project ended after five or six years, and that project successfully identified quite a number of biochemical mutations in mice, but it ultimately proved not an efficient system, and so the powers that be decided that other efforts would be done. In particular, there was particular interest in developing a number of short-term mutation tests to use sort of as surrogates for the more complex and time-consuming and expensive mouse mutation tests, and so it was simply decided at the higher levels that that was the direction the program would take. So, naturally, I became a critic, in a way, due to the fact that the short-term tests were not really, many of them at least, were not really concerned particularly with health effects or an organism that really had much bearing on human beings and adverse health effects associated with mutations. So anyway, I guess I continue to be a skeptic today, and I'm not sure . . . I guess you could say it's still sort of a stalemate, that the short-term tests really haven't established any kind of real substantial success in identifying carcinogenic hazards, and there are people still trying to develop methods with the mouse. So I don't think there's a clear winner in this controversy, even so long after the thing, the controversy, erupted.

Shostak: Staying with this for a moment, can you help me to understand the focus of your research and how it's changed over time?

Johnson: Well, I'm definitely still interested in carcinogenicity, and still interested

in the problem of identifying chemicals that cause carcinogenic effects in humans and animals. I think the better way to go, to do this, is to try to identify the genes that lead to susceptibility to the carcinogenic effects of chemicals, and I think that once you understand why a chemical causes cancer in a susceptible genotype, then you have a way of doing something about the problem, either by controlling exposure or somehow counteracting the effects. So my problem with the short-term tests and, I mean, I don't know that I -- did I give you a reprint of the paper?

Shostak: I have this one . . .

Johnson: This goes back to the early '80s.

Shostak: Okay. I don't have anything going back that far.

Johnson: But the problem I saw with the short-term tests is that there were so many of them, and they identified different chemicals as mutagens, and by the time you were done, one test or another identified almost all chemicals as mutagens. And so if you believed that the mutagens were carcinogens, then virtually everything was a carcinogen under some circumstances. And I believe the current NTP mouse data or rodent data pretty much confirms that, because as it stands, the rodent test has identified about 50 to 60 percent of the chemicals tested as carcinogens, but it only tests for any given chemical under very limited circumstances. And, for example, it uses one strain of animal, a rat, and another strain of mouse. We know that susceptibility varies according to strain, so it stands to reason, if one

can use a larger number of strains, a larger number of chemicals could be identified as rodent carcinogens. Also, the carcinogenicity varies according to dose, and it varies according to how a chemical is administered to the animal. For example, using NTP data, it's apparent that if you administer a chemical by stomach tube, a chemical is more likely to be carcinogenic than if you administer the chemical mixed up in the food and essentially force the animal to eat it. So if you use the more effective means of administration, it stands to reason that you would identify more chemicals, a greater proportion of chemicals that are carcinogens. So I did some plots looking at trends according to the data that was available from the NTP, and it appeared to me that if you doubled or, no, if you quadrupled the number of strains, you would identify maybe 85 or 90 percent of tested chemicals as carcinogens. So it kind of leads to the same place where looking at lots of short-term tests leads you. The more tests or the more kinds of tests you run, the larger the proportions of identified chemicals are mutagens, or if you look at, similarly, at the rodent tests, the larger the proportion of chemicals identified as carcinogens. So I think the NTP is kind of kidding itself that the present technology really identifies human cancers. It just identifies some, and it kind of gives you, creates in the process the false impression that chemicals giving negative results are safer than those that give the positive result. So I continue to question the value of that approach.

Shostak: One of the reasons that I was so interested in talking with you is that oftentimes, when people are critical of the traditional two-year rodent bioassay, things like transgenic or toxicogenomics are their alternative. But my sense has been that you've been very critical of transgenics, too?

Johnson: For the same reason that you nailed it. The thinking is that there is a main control gene, and if you put that main control gene in an animal, it makes it more sensitive to everything, to all carcinogens, and I say there's no evidence for that. And as far as I know, there's no one that thinks that there is a master cancer control gene, but, rather, a substantial fraction of the genome has something to do with susceptibility to chemical carcinogens. So if there are lots of genes that are behind the carcinogenic response, but in one supersensitive gene, it isn't really going to help. You know, there's -- it's a flaw in the logic. So I think the better way to go is to try to find out something about the number of genes that are involved in susceptibility. If you go down that path and you can, and you substantiate that, you learn that indeed there's a large number, then you have to look at your cancer control strategy. Does it really make any sense to say this is a carcinogen, this is not a carcinogen; it's okay to be exposed to this, it's not okay to be exposed to that; because if there are lots of genes and there are going to be some susceptible people to a lot of different things, whether they turn up to be rodent carcinogens in the test or whether they don't. So I think it makes a big difference. I think it's a serious public health issue.

Shostak: And what progress has been made in creating this alternative, the alternative approach that you're describing?

Johnson: None, or very little, let's say. And the reason is that it's expensive. Now, I think the Institute just within the past year has made some important moves in that direction. In fact, I was asked to draft a scope of work for a new contract that's going to be out. It's confidential right now, but by the time you're replaying this, it won't be.

Shostak: Okay.

Johnson: But what they have decided to do is to issue a contract to provide for a whole genome sequence, whole genome sequencing of a large number of strains of mice, and so that will provide the means to identify genetic variation that controls susceptibility differences between those strains, and down the road could help to answer exactly the question you're asking. But, of course, you also need to identify the susceptibility phenotypes to go along with that, because the genetic information alone or the sequence information alone can't help you unless you're tying it to the phenotypes you're interested in, and by that I mean the susceptibility to different chemicals.

Shostak: To clarify, when you're talking about susceptibility, you're talking about a category of susceptibility that is different than, say, the susceptibility being studied under the rubric of the Environmental Genome Project. Or are those similar sets of susceptibilities?

Johnson: Well, this would be focused on cancer.

Shostak: Okay.

Johnson: And I don't think the genome project is so focused. So, I mean, they could be, there could be other people interested in neurological disorders, for example.

Shostak: Right. I think that's right.

Johnson: Or allergy, you know, other factors where there's no… And, of course, there could be huge differences that have nothing to do with environmental exposures.

Shostak: Tell me what you mean by that?

Johnson: Well, there could be just, people could develop a, well, a birth defect, not because they were exposed to anything at all, just because there was, they just had a bad gene. Or like nearsightedness or brown hair or blonde hair. I mean, there's a lot of variability that's not controlled much or at all by environmental exposures.

Shostak: In what ways has the understanding of genes or the significance of genes changed during your career at the NIEHS?

Johnson: Well, that's hard to say. Geneticists have had a hard time traditionally at NIEHS. I had quite a number of colleagues when I came here originally back in the late '70s, and they have for the most part all left. And, of course, I'm more of a classical geneticist than anything else, and I think nowadays you have a lot of people who call themselves geneticists who

don't have any formal genetics training. You know, if you work on DNA, I guess you're a geneticist in some sense. So, but, I mean, you're not really born with the knowledge to understand how characteristics are inherited even though you may understand DNA perfectly fine. So there is a little something. It means something to be a trained classical geneticist.

Shostak: And then, from your perspective, how has the Institute changed in the time that you've been here? You must, you've seen the buildings built. Right? You've seen it all happen.

Johnson: That's right.

Shostak: I would just like to hear more about that, too.

Johnson: Yeah, yeah. Have you been to the old campus?

Shostak: No.

Johnson: Because we were in, I guess, 20 different small buildings on the old campus, something like that. I remember there was a Building 18. That's the largest number I remember of the numbered buildings, so . . .

Shostak: Does that campus still exist?

Johnson: Yeah.

Shostak: What is it now?

Johnson: You see, we, the government always leased it, and so I guess now it's private companies that have taken it over. I know some of the old temporary buildings were torn down. Some of the more permanent ones

still stand.

Shostak: So you started on that campus.

Johnson: That's right.

Shostak: And then, I imagine, moved to the south campus originally.

Johnson: Yeah, that's right.

Shostak: And now you're on east campus.

Johnson: Yeah.

Shostak: And, again, just any general thoughts or reflections about the transformation of the Institute over that time.

Johnson: Well, it's certainly gotten a lot bigger. The budget has gotten bigger and there are more people. I really don't see a lot of, in terms of quality for the day and age, I don't think it's gotten any better. I think it's stayed about the same.

Shostak: You were also here, then, when the NTP came to North Carolina, when the Bioassay Program came down and became the NTP.

Johnson: That's right.

Shostak: Did that affect the NIEHS?

Johnson: No. I didn't even really know what happened when it happened. And so, but I did, you know, as I became acquainted with it, I did spend a significant amount of time looking at the results that were coming out, and eventually did some summary tables and published some papers that cited that work. So, but I was not really an NTP bioassay person. I wasn't

really an insider in that program. I was an outsider looking in at it with some questions.

Shostak: And the larger question -- and I'll get to transgenics in a minute -- but one of the larger things that I'm also interested in is how models of carcinogenicity have changed over time.

Johnson: Yeah.

Shostak: Can you describe those transitions?

Johnson: Well, obviously there's a lot more interest now in molecular mechanisms, you know, genetic control, and, you know, if you go back into the '20s and '30s, there were a lot of very simple-minded concepts. And, for example, I mean, just off the top of my head, I recall there was the irritation concept of carcinogenesis. And I don't know. Maybe there's still some relevance of that. I don't know. But, of course, now there's, I mean, there's a lot that, an enormous amount of mechanistic, molecular mechanistic information there, and there was the viral theory of carcinogenicity, which of course, with that, there was no need for chemical carcinogens or chemical exposures. But now it's well established that there are viral causes and mechanisms are at least somewhat understood, but for some, you know, some of the carcinogenic metals, they're beginning to get a handle on mechanisms there. But I would say for the majority of chemicals, there's really still not a clue. So I think there is still a lot of room for going after the identification of

susceptible genotypes and learning about what it is about those genes that makes someone susceptible and another resistant to carcinogenic effects of different chemicals.

Shostak: And what, if anything, do transgenic models have to offer in that process?

Johnson: I think they could help confirm hypotheses. Once you think you have the gene, well, then, then you can take that gene out of a susceptible, put it into a resistant, and maybe turn a resistant into a sensitive, and that would be sort of the final proof that, hey, you've really got the gene. So I would think that that could be very important hypothesis testing and confirmation down the road. But I don't see them as useful for prediction in the absence of knowledge of what the genes do.

Shostak: Okay. Are there other significant limitations of the transgenic models that you would call to my attention?

Johnson: Well, I think a single transgenic model might be considered inexpensive, and if you have just one, two, three, or a small number of genes that determine susceptibility, then it might be an economical approach for testing chemicals. And if you have a thousand genes, then I don't think you can call it a short-term, inexpensive alternative test, where it becomes more, a lot more expensive than the conventional bioassay test. So I really don't see, at the present stage, I don't see them as an efficient means of identifying chemical carcinogens.

Shostak: What would you say has shaped the development of the agenda, the

research agenda, on gene-environment interaction at this point?

Johnson: What shapes it?

Shostak: Yes.

Johnson: What shapes gene-environment interaction, or interest in it?

Shostak: I'm thinking about the scope of work that you were just asked to write. What were the factors that lined up such that that would become a research area?

Johnson: I don't know. This was an administration proposal. It came from the Office of the Director to help us draft a scope of work for this… like it's a direction we want to go kind of thing. So I thought it was a good idea, so I was quite happy to do what they asked. But I really, I really don't know what the thinking is. And, you know, we're at a stage where the Institute can change drastically in the next two years with a new director coming in.

Shostak: How many directors have you seen at the Institute in your time here?

Johnson: Well, when I got here, David Rall was the director and there was Ken Olden. Those were the only two I've known.

Shostak: Okay. And did the Institute change significantly when Dr. Olden became its director?

Johnson: Well, it became more molecular, certainly. I'm not sure how much of that was due to Ken Olden or just changing times at the NIH generally, because I think all of the NIH changed during this period.

Shostak: What contribution does becoming more molecular have to the larger public health issues that you've been referring to?

Johnson: Well, it has to do with understanding what's going on in the body. I mean, this applies to whether it's disease organisms or just environmental chemicals, contaminants, things like that. I mean, what you see on the surface is, you know, someone is uncomfortable, becomes ill, or something like that, but once you get inside and you see what's happening in real detail, and once you see that, then there's a chance to do something about it. So, you know, it's just a deeper, more profound understanding of what's going on.

Shostak: Does having a more molecular understanding lead towards a specific set of interventions?

Johnson: I'm not sure if it does. I'm not really sure if it does. But what it does do is help you see the effects of exposure maybe at some stage before people actually get sick, you know.

Shostak: I'm curious about what interactions, if any, you've had with the regulatory agencies about your research.

Johnson: Well, I picked a little bit on the FDA and EPA.

Shostak: I've noticed the picking on the FDA in your articles. I didn't see that. It must have missed the ones with EPA.

Johnson: Well, a little bit later one was -- let's see if I can remember -- how many high-production chemicals are chemical carcinogens, that one.

Shostak: Yes.

Johnson: So, the high-production-volume chemicals are the purview of EPA, so I thought when I asked the question with respect to food additives, you know, can make the same point with just chemicals produced in large amounts, because, you know, generally, those are going to be the ones that humans get exposed to. And so, again, just looking at high-production-volume chemicals tested by NTP, it looked like some 60 percent were carcinogens. So if you've got -- I forget what there are, something like 3,000 high-production chemicals, but vast tonnages, if half of them really are, or more than half really are carcinogens, that's a pretty serious control problem, exposure-control problem. If the bioassay is just misrepresenting the hazard, then that's another matter, you know, and I think there's a good chance that that is the case. But I don't know, I don't know. You know, the real question is the low-dose exposure. It may well be that you can, that with a high enough, high and long enough exposure, you can make animals come get cancer eventually in their lifetime, but perhaps at low doses it's very difficult. And, of course, since the NTP bioassay is basically a high-dose, long-term assay, I mean, we don't know. So that's the other question: what are the consequences of these low-dose exposures that most people are involved in? Maybe not much, but anyway, I guess it's these high-dose effects that have been running this, driving this program since it started in the '70s, first at NCI.

Shostak: When I first mentioned transgenics, you said they tend to be controversial. How would you describe the nature of that controversy?

Johnson: Well, there's quite a number . . . I would just say that you don't have to look very hard to find critical papers in the literature. And there are advocates, and it's pretty easy to identify the advocates as well. But when I started criticizing short-term tests back in '75, I was alone because it was a real wave that started about 1971. So I was swimming upstream pretty much alone back then. But now, there are still advocates for short-term tests in general. I mean, there is some hope that someday short-term tests will be developed to replace the bioassay. But at the same time, the transgenic short-term approach has its advocates. But it's obvious that there are critics of that approach out there, too.

Shostak: In terms of the science, how would you describe the difference between the positions of advocates and critics of the transgenic tests?

Johnson: Well, a lot of the advocates have laboratories and careers that depend on this work continuing, so, you know, there's a vested interest. It's not a purely objective, any kind of thought that drives this thing.

Shostak: I'm thinking about my own field and thinking the classic conflicts between groups of sociologists, and often there was an underlying difference in analysis or difference in analytic approach underlying different vested interests.

Johnson: Sure.

Shostak: So, again, perhaps to push the issue are there any fundamental differences in the way advocates or critics of these tests understand the process of disease production?

Johnson: Not that I know of.

Shostak: Okay. That's interesting. From your perspective as someone who's spent his career in the environmental health sciences, broadly construed, what, if any, do you view as the most significant accomplishments of the field?

Johnson: I don't know. I can't point to any particular watershed. I feel like I've made some progress. I haven't really gotten the program going in the direction I would like to see it go, but there's a little bit of bending, I guess.

Shostak: Then let me ask what the most significant unmet challenges are at this time.

Johnson: I guess I'd like to see a solid program aimed at identifying susceptibility genes in mice, and then having found them in mice, having them identified in human beings. That's where I think it needs to go.

Shostak: How would information from that program would be translated into environmental health and public policy?

Johnson: It's hard to say. It depends on the results. Once you know a particular gene is involved in a particular susceptibility, then you can really get at that dose question. And it's not just susceptibility, but it's dose as well. And I think once you have some understanding there, then you have some

knowledge that can be useful for policy decisions.

Shostak: I think that we touched on all of my questions. But let me ask you if there are aspects of this larger area that we haven't taken up that you would direct me to.

Johnson: Well, in terms of the bioassay, the way it's done, I think there are people that think that it needs to go forward pretty much the way it is, and there are probably some pretty strong advocates for the bioassay out there. I'm, of course, not one of them. But, I mean, to be fair, you really ought to talk to them and let them persuade you.

Shostak: What I observe just so far is that folks who advocate the bioassay as it is advocate it as the best thing we've got, not as a perfect system.

Johnson: Yeah. And what I'm saying is, I understand that. What I'm saying, though, is that it may not be any good at all, and you really ought to look closely enough at it to make sure that it's doing what you think its doing rather than just being led down the garden path.

Shostak: Right. Would it be helpful, then, to also have kind of more epidemiological data on human cancer and cancer causation?

Johnson: Yes, but epidemiology is such a blunt instrument, so it's difficult.

Shostak: I read the article you had in *Mutation Research* in 2002, which was on the high-production-volume chemicals, and you say in the conclusion to that article that there are serious flaws in the system, and you tie it back to the war on cancer and the ultimate public health mission.

Johnson: That's right. It gets back to politics, doesn't it?

Shostak: Well, of that vision for what preventing cancer would be, and I was just thinking in reading that that one of the stumbling blocks, then, I mean at a policy level, is the wider argument about what accounts for cancer prevalence in human populations.

Johnson: Yes. But it's-the-best-we-got argument is very difficult to deal with. If you're arguing at that level, well, you know, that's a hard place to argue.

Shostak: Right. And it's interesting. I talked to some people in the Center for Drug Evaluation and Research at FDA, and I know you've been critical of FDA, but some of those folks actually are saying things very similar.

Johnson: I know they are.

Shostak: To what you're saying.

Johnson: Thank God in a way.

Shostak: And the way they would say it is, you know, the bioassay is called the gold standard of toxicology testing, but that's actually a horrible misnomer.

Johnson: Sure.

Shostak: It's just the only standard.

Johnson: Right.

Shostak: And that's similar to what I hear you say.

Johnson: Yes, it is.

Shostak: Okay.

Johnson: Yeah. And it's a standard in the sense that they always do it, whenever they test a chemical, pretty much the same way, you know. Its 50 males, 50 females, a C3H. But anyway, a standard strain of rats, a standard strain of mouse, two years. So it is a standardized test more or less. It's always at least three doses, you know, a control and a low dose and a high dose at least. Sometimes it's more. So, and then it's very carefully monitored. Animals are examined very carefully and data is recorded very carefully. So in one sense, it does deserve the name gold standard because undoubtedly they try to do a careful job, and it's expensive, you know. It's $5 million to test one chemical, at least. It can be $10 million. And then if you look at all literature dealing with detecting cancer in animals, you see that. Well, sometimes a guy will view it as 10 animals, and sometimes five animals, and sometimes this strain, and sometimes that strain, so there's just horrible heterogeneity in the literature. So the NTP did try to focus in and give us a standard method and then apply it on a regular, routine, standard. It was genetic variability in a carcinogenic response. And they didn't know that there was going to be variation, according to how the chemical was administered. But then they discovered the few times that they did a different route of administration, that they got different results. So it then became apparent that there's not just genetic variability; there's variability in the method that can give you different results also. So, you know, you put that all together and then you

have a result that half of tested chemicals are carcinogens. Well, what if you used the other strain or the other route of administration? You might have 90 percent. And if that's the case, I mean, it's going to be hard to do anything about control by labeling a chemical a carcinogen.

Shostak: What's the alternative control strategy, or what's an alternative control strategy?

Johnson: Well, again, we have to know about dose before we can say. But if everything is a carcinogen, then you have to be exceedingly careful about exposure.

Shostak: And that's why that would be such an expensive…

Johnson: Sure, that's right. And that's why the regulatory agencies don't want to think that.

Shostak: Right, right. Their jobs become much more difficult. So would you say -- and what I'm hearing in your descriptions is that you have a very public-health-driven orientation to doing this research.

Johnson: Well, yeah. I mean, that's why I decided to work here.

Shostak: It's interesting to me, especially as it seems like one of the things that makes the NIEHS a little distinctive is that the focus is more on disease prevention and public health. Does that resonate with your experience here?

Johnson: Well, I think, I certainly think you have individuals here who take that seriously, who take, you know, consider environmental health important.

But actually, I consider health of the environment, environmental health as well, so I don't think you have to just look at human effects to consider health of the environment.

Shostak: Actually, I noticed you have marine toxins in toxicology [NOTE: these are books and articles on his shelves]. So, you have a broader focus, then, than a lot of folks do.

Johnson: Well, I'm practical minded. I'm not too keen on just studying things in a test tube because it's fun. I do like to see relevance.

Shostak: Anything else that I should have asked that I've not?

Johnson: I don't know. Ask me anything you want.

Shostak: I have.

Johnson: So, where are you going next?

Shostak: I am talking with Sam Wilson at 3:30, and then I am going back to my hotel room to get ready for tomorrow's set of interviews.

Johnson: Well, say hi to Sam for me.

Shostak: I will.

Johnson: Sam is the guy, I believe, behind the sequencing program, so you'd better ask him the significance he sees in the genome sequencing to environmental health and see what he says.

Shostak: I will. Actually, most of my questions for him are about trying to get at his perspective as an administrator of the Institute.

End of Interview