Interview with Dr. Samuel H. Wilson

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Research Triangle Park, NC
January 20, 2004

[…general ongoing discussion about new initiatives in Environmental Health Sciences using mouse models and an appropriate title for such activities…]

Samuel Wilson: [The phrase "genetically modified mouse models"] is . . . too restrictive. This point is actually related to one of my concerns, because inbred strains that are already available in the larger repositories, like Jackson Labs, can be used in and of themselves, without direct "genetic modification." And so, this approach needs to be accommodated within a title also.

Sara Shostak: Okay.

Wilson: Something more general like "mouse models" or even animal models might be better, leaving it open as to what the definition of animal is, because this would be broad enough to accommodate alternate groups of organisms and also to do proteomics and systems biology initiatives in the future; whereas if one limits work to the mouse, then the idea of systems biology is way, way out there in the future, on the other side of a distant planet type of situation.

Shostak: So then, if we take your concern about the title as a point of departure, what is the range of initiatives that you would want to see included in an assessment such as this, if it was no longer limited with the word

transgenic or genetically modified?

Wilson: Well, I think that the idea of using genetics, in the classical sense of defining requirements for phenotypic outcomes, in order to document those requirements, is incredibly important for the field and for the work of this Institute. So, mouse experiments that allow us to use mouse genetics would fall under that category of genetic uses; other types of genetic experiments need to be done also, in yeast and bacterial model systems and other kinds of animal systems like *Drosophila* or marine animals or *C. elegans*, and so on. But, the concept of utilizing genetic approaches is so important that we need to think creatively about ways to foster this more robustly and to incorporate these kinds of experiments into our fundamental planning. So, this critical point about the importance of genetics is one feature that triggers this notion of having a broader title. In general, I think our field will need to do a lot of additional "discovery research" before we can make use of improved animal models in hazard assessment, for example, in the National Toxicology Program or in other types of translational toxicology approaches. So, the continued investment in these types of fundamental research, discovery-oriented programs, is very, very important.

Shostak: As an observer of the NIEHS over the past several years, it seems that the Institute is pursuing major transformations in what it means to do environmental health science. And when I say that, I'm thinking about the

Environmental Genome Project, the National Center for Toxicogenomics, and in some ways the pursuit of research using genetically modified organisms. How did these agendas emerge? What did they come up from?

Wilson: Well, I think this has been a function of changes the broad field of molecular biomedical research, basically as embraced in all of the NIH institutes and centers, and the availability of molecular biology resources and molecular biology approaches that have enabled manipulations of cells and tracking of such manipulations along with phenotypic outcome measurements. The ability to do all of this has created a Renaissance, really, in biological research. I think this factor, more than anything else, is the reason that Environmental Health Sciences research has moved along these lines in recent years, as you have noted in your question. The overall questions we are addressing in the Environmental Health Sciences are not different now compared with 30 years ago. It is just that this Renaissance has given us much more precision with which to ask the time-honored questions. So, I think the changes are a reflection of the Institute's ability to keep current and to keep its fingers on the pulse of what's going on generally in biological research.

In this context, of course, our challenge is to translate this progress related to enhanced research capacity to the field of toxicology. And this is

something that just happens naturally, as we achieve recognition in the field as to the effectiveness of new experimental approaches and experimental opportunities and so on. So, I don't really see the leadership aspect as implied, I think, in your question so much as this feature of the how the entire field of biological research has changed and the manner in which people in our portfolio at NIEHS have changed in step, are publishing in the same journals, and are undergoing the same types of peer review as the other scientific communities across the NIH. So, consequently, our research community at NIEHS is held to the same standard as the communities of the other institutes, and therefore, similar experimental approaches and concepts are being used. I just think this is a reflection of an orderly and natural evolution toward more precision for the scientific community in general and in toxicology. It's true that there are a lot of differences, a lot of changes, let's say, when comparing the research in our portfolio now and with the research 20 or 30 years ago. But, that is primarily because of this feature of "evolution" in biological research.

Shostak: How would you characterize the differences in the portfolio between now and 20 years ago?

Wilson: Well, there is much more emphasis today on molecular mechanisms of toxicology, from the standpoint of identifying metabolic and macromolecular changes that are closely associated with the toxicity

outcome, and I would look to see this approach become even more integrated into the portfolio, much more tightly associated with our research investments, over the next 20 years. And, I perceive that this emphasis on molecular mechanism represents a big difference, comparing 20 or 30 years ago with today; also, I think the field of epidemiology- although I don't know this for sure- has expanded over this period and has incorporated certain molecular approaches such that "molecular epidemiology" is now becoming a sub-section of the broad field of epidemiology. I see this use of molecular endpoints in epidemiology as a change, and this feature is probably one that that will become a lot more robust in the future. I think some features about our portfolio that haven't changed. For example, there is the need to educate young scientists. For some sectors in the community, such as industry, we have a responsibility and special role to make sure that the next generation of practicing toxicologists is trained to the best of our ability. I think this feature has held pretty constant. And, the overall need to do fundamental research in toxicology has held constant. We're a lot bigger today than we were 20 years ago, so this represents a difference. But, we still share a commitment, in the NIH style, to emphasize fundamental research. And, over the last 20-year period, there's been a change in the way that our center programs operate, in that there is much more emphasis today on the holistic features of the Environmental Health Sciences, so that the ideas of

"community outreach and education" and actual research-education partnerships with the local communities are occurring and working very successfully in the portfolio today, and I don't think this was at all true 20 years ago. I think the scientific approaches at our disposal, by virtue of them being more precise, represents a difference. It's much more common these days for people to do multidisciplinary or interdisciplinary projects, even under the support of one RO1 grant, such that an investigator might combine three or four different hardcore disciplines, all within the context of one research program. This widespread use of interdisciplinary collaborations has changed a lot. There are good things and bad things about this, but it does represent a change, and this feature makes it more challenging, in a way, to do research these days than 20 or 30 years ago.

Shostak: You mentioned the changes in the scientific field as a core engine that drives the development of new practices.

Wilson: Right.

Shostak: Are there any other factors that you would point to as significant to the changing practice of environmental health research?

Wilson: Well, I think one really big factor has been the expansion of the NIH budget. Using the arbitrary framework of 20 years, one thinks back to the early '80s: the NIH budget was not doing so well during that period, and things were pretty tight. There was a general recession in the country, as

well, and we, as a group in biomedical research, had not begun to think in a really robust way. We hadn't really achieved a point where we could grasp that there would be an explosion in DNA research and in molecular biology research. At that time, DNA sequencing was just coming online, and the idea of making use of recombinant DNA technologies was just beginning to penetrate, take hold, at that time. And, I don't think people really got the idea that we were entering a true Renaissance until the mid-'80s or possibly between '85 and '90. By that time, a lot of scientists sort of "got" the idea. My own experience was a case in point: I started working about the same time (the early 1980's) on these molecular biology approaches toward solving traditional biochemical problems. I mark this period as the beginning, or seed, of the Renaissance, that has occurred. I think it's a very different scientific world today than it was 20 years ago, fortunately.

Shostak: What would you describe as the kind of ultimate vision or the end goals of a molecularized approach to environmental health science?

Wilson: Well, the idea of understanding biological stress-response pathways in a truly "engineer's view" and, the ability to do this in many species, is one way of articulating the endpoint. So, it's this knowledge base of networks inside the cell that will allow us to understand the exposure-disease paradigm that I'm talking about here. Now, what public health impact would this knowledge have? Well, it could have enormous impact in our

ability to understand dose-response relationships and why there are tissue-specific differences in responses in human beings, why there is individual susceptibility, and why there are developmental-stage specific responses. So, by having that information, if we could understand those kinds of things, then we could control exposures and better understand how interventions might work or would work. I think that the questions in toxicology, the field of toxicology, are fundamental to this more science-based and systematic approach to controlling adverse effects from exposures. In other words, there would be a huge, revolutionary effect on public health if we could achieve a precise understanding the classic exposure-disease diagram or flow diagram, as to what happens after hazardous agent exposures. But, there is a large information gap at the moment, that is, a gap between our level of understanding at the present time and what we need to know in order to be able to complete the exposure-disease diagram. This information gap notion is what frames my thinking about the field of toxicogenomics, or genetic susceptibility, or specific exposure adverse-effects concepts; it is just incredibly impressive how much we do not know and how much we still need to learn in order to be able to have a logical, really systematic understanding of the exposure-disease paradigm.

Shostak: What contribution, if any, might genetically modified models make in this information gap?

Wilson: Well, taken to the extreme, they can allow us to complete this hypothetical engineering diagram of biological responses I am talking about, or at least contribute to it significantly. This is because research on genetics in an animal model will be the closest we can get to understanding genetic factors in humans on a robust, systematic basis. So, a very active reasarch program in mouse genetics that would, for example, relate to a human toxicology situation, could be incredibly important toward allowing us to understand the repertoire of requirements (or genes) involved in each human adverse effect. Let's say, for example, there would be 20 such requirements for each adverse effect, and that the reason for each requirement could be discovered, in terms of the macromolecules and the biological pathway connections that causes the requirement. I think this is the most logical way to think about the utility of mouse models, as contributing toward filling in the information gap concerning pathways leading to adverse effects. More short-term endpoints, like achieving greater toxicant sensitivity in an animal model and so on,, are not a part of what I'm thinking about here. I'm thinking instead of how to fill up the immense information gap in our understanding of biological responses to toxicants. The issue of hazard assessment testing and sensitivity is much more straightforward; it is a challenge that is much easier to approach. We can already design animals that are hypersensitive to toxicants by knocking out some type of protective mechanism. So this type of

application of animal models is going to happen, and this clearly will be a part of the Institute's effort. But, this is a relatively near-term type of animal model application, compared with being able to understand how many requirements for an adverse effect there are and whether or not the requirements are the same in humans and in test animals. This question of how to predict whether or not there will be the same requirement in humans and animal models is important, and the answer to this trans-species comparison challenge will be obtained through developing knowledge about pathway differences across species. The questions in trans-species comparison are similar to the questions posed in the Environmental Genome Project. That is, individuals have the same set of genes, but these genes are functioning in ways that are sufficiently different to yield differences in individual susceptibility. The same picture is true for comparing susceptibility between mice and rats, or between mice and other animals. So, by making use of rodent animal models, we hope to deal with the information-gap problem.

Shostak: The Environmental Genome Project has a mouse genetics consortium component.

Wilson: Yes.

Shostak: Can you help me understand how it fits into the larger Environmental Genome Project?

Wilson: Well, the long-term goal of the Environmental Genome Project is to

facilitate molecular epidemiology research in humans, molecular in the sense of using exposure measurements, as well as genetic or DNA measurements. Regarding genetic measurements, the question of understanding mechanistic implications of genetic features observed is what the Comparative Mouse Genomics Centers Consortium is all about. It is an effort to promote functional genomics research in the mouse toward understanding the significance for human gene variations. This work is being done by "humanizing mice" through transgenic knock-ins, and then by studying the function of a human protein in the mouse background. Alternatively, a mouse gene is surgically altered so that it has the same variation as the human gene of interest, and then the mouse is examined for function of the altered mouse gene or gene product. All of this work is conducted in the context of toxicology, from the standpoint of understanding the effect of the gene variation on a toxicant dose-response relationship. Creating the mouse model with which one can study this kind of relationship is what the Mouse Genomics Consortium is about. So, yes, it is part of the Environmental Genome Project in the sense that it informs us about functional genomics of SNPs and other DNA variations. And, the Consortium is doing its work in a way that recognizes the importance and wonderful surprises that are inherent in animal genetics, that is studying an animal with the realization that we don't know enough yet to really be able to predict what the outcome will be in such a complex

biological system. The idea of using a whole organism, a whole animal, with various differentiated organs expressing such an altered protein, is going to yield a lot of surprises, surprises that we are not able to anticipate at all.

Shostak: And then, what role, if any, do genetically modified mouse models have in the National Center for Toxicogenomics?

Wilson: Well, in the case of Toxicogenomics we're looking at genome-wide expression, of course. Once the expressions are categorized in a baseline way, then one needs to have a ways to provide perturbations or alterations in the biological system under study. One can imagine doing this with chemicals. Or, another way is by altering the genetic background. Hence, these models developed by the Mouse Consortium will fit into the Toxicogenomics initiative, because the models will represent approaches toward altering the genetic background or the gene-expression capacity of the system. In other words, I see the use of mouse models and Toxicogenomics as part and parcel of the same scientific theme. Any techniques that we can make use of, like RNAi knock-down libraries.

Shostak: I don't know what that is.

Wilson: It's a strategy where we can eliminate a specific messenger RNA, in a sense in a surgical fashion, such that the approach is equivalent to knocking out a gene by gene-deletion, except RNAi just knocks out the messenger RNA.

Shostak: Okay.

Wilson: So, use of RNAi is another approach to altering the gene-expression function of a gene. This is where I see these transgenic mouse models coming into the Toxicogenomics effort. More broadly, it's a way to have systematic genetic variation and to use that variation to understand the significance of expression patterns as a function of toxicant exposure.

Shostak: Okay. We talked a little bit about the factors that are contributing to the emergence of these new approaches and what's exciting about them. Is there significant resistance to this vision of what it might do to environmental health science?

Wilson: I don't think so. I think that the field in general -- and that would be defined as the field of toxicology -- has embraced the new genetic and genomics features in a very robust fashion. I don't detect any real reservation about this, except recognition of how daunting and complex the notion is. And, there's always a big push to apply new science before it's ready to be applied; that is also a concern in very general terms. But these concerns will be worked out in relatively straightforward ways, say, over the next five to 10 years. But, filling these information gaps I talked about earlier is much more long term, and the scientific community doesn't seem to be put off by that. The community has embraced the genomics approaches and is settling in for a long period of systematic investigation, to be able to make use of all these new opportunities

afforded by genomics. On the topic of reservations, I think there is a lot of reservation about using a broader definition of environmental health sciences, because in this way we are now working with a definition that includes topics like obesity and . . .

Shostak: The built environment?

Wilson: Yes, the built environment, behavioral factors, and a whole range of topics that did not fall under a more limited definition surrounding exposure to chemical toxicants. Some of our colleagues in the chemical-toxicant arena, I sense, are not so pleased with the use of this broader definition of environmental health sciences. But, that issue is the main reservation I have encountered. It appears to me that the general picture is almost the opposite: People are so enthusiastic that it's kind of like, hey, guys, let's settle down here and not get too carried away, and lets "stick to knitting" in terms of understanding what we're doing. So, I haven't heard significant reservations as yet. But, we should be realistic about the situation. We are a funding agency, and so people are generally happy with what we're doing, as long as there is good funding. As the NIH budget goes to a more flat pattern, as we expect, then the Institute is going to come under a lot more pressure, I predict, as to priority setting and whether we should be doing this or that, or whether we really have enough resources to support some of the projects that were started up during this past 6-year period of very favorable budgets. But, we haven't gotten into

that phase yet, either. I suspect that in the next year or two years, this question you ask is going to be a lot more relevant.

Shostak: Sociologically, what you're describing is really interesting to me because you're talking about both scoping out and scoping in. Right?

Wilson: Yes.

Shostak: So, you are including a more social and behavioral definition of environmental health at the same time that you focus on molecular mechanisms that lead to environmental illness.

Wilson: Right, right.

Shostak: How do those two things co-exist? Is there a dialectic there?

Wilson: How do they co-exist? Well, I don't know. I mean, in a sense, there isn't disconnect. There isn't a dichotomy in the sense that the NIH needs to be able to offer benefits to the public and to communities and interest groups and so on. NIH needs to be able to communicate the benefit to them. And, at the same time, our (NIH's) culture and historical method of doing research has been to understand basic mechanisms and to make use of that information in translational approaches that benefit public health. We need to do both. We need to communicate to the community and explain what we're doing and how it benefits them. And, NIH scientists' views of the various facets in the human health arena, like the role of the regulatory groups, the role of the international trade functions, the role of the public health functions (like the CDC and state public health functions), can help

interpret to the public how this entire enterprise works together toward benefiting human health and how the NIH has an important role to play. I don't see why NIH shouldn't reach out and take on this communications burden, being able to communicate these various features, and at the same time realize that our core approach is to contribute a certain type of fundamental research information and scholarship on these health problems. And so, I understand that you have a really good question, a really good point there, but on the other hand, there's no reason for this point to represent a disconnect or activities that we can't blend, you know, these are two different types of activities that should be blended. NIEHS has been encouraging its grantees, especially in the larger programs like the centers of excellence and so on, to adopt this kind of outreach attitude, to invest a little bit of their energy and time in trying to refine skills and to come up with the communications devices to be able to be effective in public outreach. So, yes, I agree, your question is interesting. I think it is possible to blend both types of activities, and I think doing this enhances us as a group, the NIH as a group. We need to find ways of reaching out to the public concerning real-world problems, while not losing track of the fact that we're charged to discover fundamental mechanisms of disease and prevention to gain fundamental understanding about biological processes. So, we must not let these outreach activities, these other things, cause us to become distracted or really to redefine our culture or what we

can most effectively contribute.

Shostak: Are there models for the kind of comprehensive advances you're talking about, or is the NIEHS in fact developing these models?

Wilson: Well, I don't know, lets see. I think the NIH itself has been a model, in my time at the NIH, of having a more holistic view of human health and realizing that it needs to conduct fundamental work to understand ways of taking major advances forward, and at the same time keeping its focus on the public health needs. So, I think NIH, historically speaking, is a good model for this kind of thing. And, when I look at other agencies in the U.S., I don't think there's the same kind of blend of really outstanding, fundamental knowledge building and at the same time, a recognition of the need for translation and the need for a holistic way of understanding the public health burden. Just look at the Heart and Lung Institute and all the contributions they have made to understanding cardiovascular disease risks in the population based on the Framingham Study among many others, and in addition, all of their public education on the importance of cholesterol and blood pressure and regular checkups and exercise and the whole nine yards. It's amazing. That contribution has come from the Heart and Lung Institute, and it's just a wonderful example of a model where they've blended the public health aspect of the mission of the NIH with the fundamental science mission. They have some of the greatest success stories in fundamental research of all the NIH institutes. So, I

think NHLBI is a good model. The NIH overall is really a good model for this kind of blending, as well. Therefore, I don't think NIEHS is, by any stretch of the imagination, out in front on this kind of thing.

Shostak: From my perspective, one thing that makes the NIEHS different in this regard is its relationship to the National Toxicology Program.

Wilson: Right.

Shostak: And the other sorts of public health interventions which it therefore contributes to.

Wilson: Right.

Shostak: Which leads me to be curious about your vision of how and where the NTP fits into all of this.

Wilson: Well, I just think the NTP is a terrific translational research product that this Institute can be very proud of. I think a lot of the institutes have similar types of translational components. The NTP is a sub-category of a broader policy-informing role the Institute has. In the case of the NTP, this role has evolved to be mainly hazard assessment so far as cancer is concerned, and this is a somewhat limited kind of expectation. So, the NTP is not everything to all of our policy needs, but it is one of the really blue-ribbon activities we do here at this institute very successfully. But, I think this question of informing policy makers is a really interesting one. An interesting aspect surrounds the notion that "just a little bit of information goes a long way" in informing policy… just one great

experiment that can stand up over time can have a huge impact on policy. Therefore, we don't have to have or need a complete biological wiring diagram in the field of toxicology to be able to impact policy. You know, we don't need the ultimate complete understanding of a hazard response, but instead good, solid scientific information will go a long way in informing policy making. In our society, it doesn't take a lot of such information to actually spark public policy action. And at the same time, even though this feature is good news, it also puts a certain burden on the Institute to, first of all, develop this kind of information, and, secondly, to make sure that the quality of the information is extremely high. Thus, we need to make sure that the process of conducting science really does end up in producing information that is impeccable. This discussion sort of feeds back to the questions of precision in our research, and how can we marshal instruments of maximal precision to be able to do science that forms a stepping stone toward the ultimate discovery of mechanisms of biological phenomena, and at the same time, is solid enough so that policy can productively be developed from it, incrementally, as we go along.

Shostak: It speaks to your concerns about translation also. It means that the Institute needs to be involved in kind of the meaning-making that surrounds scientific experiments and new technologies.

Wilson: Yes, right. I think a lot of us have that sort of perspective on a role of the Institute. That is, a concept of developing process, scientific process, as

we go forward. And, of course, there will be incremental discoveries, refinements, and changes along the way. But, the better the process, the more solid and informative the process, and the less subject it is to artifacts and to misinterpretation, the better the Institute's contribution will be. So, thinking about research in this way changes the optimal strategy a little bit. Take the example of exposure to toxicants: "What's the best way to do science on this problem?" This is an example of a very interesting, challenging, and broad scientific management problem.The same features are true with genetic susceptibility. I think the question has been solved for the time being as to what we should do about understanding individual differences in susceptibility? But a few years ago, we didn't know the answer as to how we could solve this problem through better scientific management. And, there are a lot of other examples of this same type of challenge for the Institute. This is an interesting way of thinking about science management. I think you're right there.

Shostak: Because some part of the definition of environmental health does focus on chemicals in the environment, and because of the relationship between the Institute and the NTP, my perception is that this Institute, perhaps more than some of the others, has interactions both with activist organizations and with industry that are unique. And I would like to hear your perspectives on how the Institute's culture, that's the word that you've

been using, is shaped by those sets of interactions.

Wilson: Well, one overriding feature in our field is that use of scientific information for policy is a very conservative enterprise, and similarly the use of assays for hazard assessment is very conservative. This feature creates a different set of milestones and time-lines than those we typically use in more basic research. For example, in basic research, we expect a scientific field, over time, to achieve consensus and eventually validate information and the methods used to develop it; whereas in toxicology, regarding these translation/ implementation areas, we don't do it that way. We actually try to circle the wagons, and over a limited time-frame say, "Okay, let's get this assay defined as a very solid type of approach and get everybody to agree on this, and then we'll go forward using such a validated assay." And, the points of information that we develop in the field that are the basis for policy, once again, are very conservatively viewed and debated, but this is generally over a limited time-frame (one to several years only). So, this is a feature of our field that a lot of other fields don't have. Well, why do we have this feature? It's because of the interface between industry and policy development, where industry says, "Wait a minute. If you guys put in that assay, this is going to confound things and it may ultimately do harm to our society rather than good." So, we need to be really, really sure that a proposed new assay works or that the scientific information developed can be interpreted usefully and is

solid. I think this dynamic is a key feature of our field. It is a paramount point that must be accommodated, and we need to understand this point because it's so fundamental. The origin is the dynamic between industry/economic development and the concept, on the other hand, of preserving the environment and, of course, preserving the environment in the context of achieving economic well-being and vitality; fundamentally, there is not a disconnect here. It is just that we need to work in partnership as we go forward, and this is where the science comes in; industry does not want to have practices or products that harm people. Industry does not wish to end up in a situation where they have contributed to environmental degradation, so they need the scientific information, as much as the environmental protection community. Both communities need the information. It's just that when things get out of whack regarding the status of the scientific information that we have a real problem. This circumstance doesn't serve either community or the nation very well. The bottom line is, we need more science, a lot more science, and unfortunately our field is relatively under-funded, under-supported, to be able to provide the wealth of information needed. And, of course, this is a circumstance that many of us in the field are worried about. We just don't have the amount of research underway that is necessary to fill all these needs. But, I think you hit on a point with your question that highlights a special feature of our field: The dynamic between industry

and environmental protection, because this dynamic has created the drumbeat we work with and the framework we use. This feature is very different than my perception of most of the other NIH institutes and extramural constituencies, because they can do their research via the classical scientific approach and don't have this sort of overriding pressure for validation/precision on a short time-frame. This difference is interesting.

Shostak: I think it's fascinating.

Wilson: It's fascinating, yes. It really is fascinating.

Shostak: A couple of questions that are more requesting your personal reflections. You came to the Institute in 1996. Correct?

Wilson: That is correct.

Shostak: What have been the most significant changes in the Institute during your time here?

Wilson: Well, I think topic of the working definition of environmental health sciences is one of the changes. Even though the definition has always been broad, I think the "working definition" has become broader during this last 8 year period. A big change has been in the budget the Institute has to work with; it's over 2.5 or so times the size it was in 1996. The attendant increase in the research program has been very exciting to observe. I think the idea of communicating more effectively with the public has been another change, and we are still enjoying this theme a lot

and wondering where it is going in the future and how it will do in the "test of time." Another change I've noticed is that the scientific productivity and the scientific quality of the portfolio are higher today than in 1996. The Extramural Division has done a good job in fostering this kind of evolution toward more outstanding scientific contributions. Their Program Analysis Branch is an example of one of the innovative things they have done to assess, in a more quantitative way, the productivity of the portfolio. I think this advance is exciting, a sort of measurement-oriented grants management philosophy. Pretty exciting! It's very challenging, of course, to quantify and measure scientific productivity, but undertaking this perspective and moving in this direction is what I find exciting about what they are doing with the Program Analysis Branch.

Shostak: Is there any related or associated effort to look at the translation of all that scientific productivity? Actually, this came up in an interview earlier today. Someone asked, "Well, how do you assess public health impact of a scientific portfolio?" and I didn't have a good answer.

Wilson: I don't think so. I believe we struggle with this challenge a lot and try to put the best spin possible on the translational impact. But, as to an effort, an organized effort, such as there is for publications and bibliometric analyses, I don't think there is such an analysis concerning the level of public health impact. There could be, however. In a broader sense, we

could use public health indicators as both an indicator of environmental degradation and how successful the research/health community is in protecting public health. This is an approach some of the leaders in the field have been interested in, and this probably needs to be pushed much harder in the future. One thing about this approach that I like a lot -- and I'm digressing a little bit -- is that we can measure health status precisely, whereas we can't measure environmental hazard exposure very effectively at all. But, we can ask, how many people have diabetes, how many people have Parkinson's, cancer, and on and on, in each segment in the country, and then we could accumulate all the information. In this fashion, we would be able to appreciate trends and patterns that will be useful over time. So that, it seems to me, this capacity also could be used to answer your question about translational impact assessment, and also to answer the question, what is the exposure status in the country?

Shostak: It would be marrying the NHANES type survey to a GIS approach, right? Those would be the two kinds of things that would need to come together.

Wilson: Right, on a national basis. We could have a GIS map of the country and, using it we would be able to understand, for example, that cancer is going up or down, or that diabetes is going up or down. I mean, there are a lot of chronic conditions that have been described recently as being an epidemic. Well, is this really the case? And, are there special features/geographic circumstances where such a trend is true and others where it isn't true. I

mean, what do these claims about epidemics and health status really mean? Right now, there is a lot of hand-waving in this area. But, I wish we had a way of precisely tracking health status across the country.

Shostak: And spatially.

Wilson: Yes, right.

Shostak: I'll be very, very interested to see how the Institute starts incorporating those approaches.

Wilson: Well, NIEHS has begun to work on this approach. For example, we are partnering with the USGS on a pilot project to do just this type of national exposure survey with methyl mercury exposure. But, achieving such a national map of health status and exposure assessment will be a long, difficult road, and this is unfortunate. We don't have the necessary medical surveillance data at the moment, and we don't have the exposure data. So, one must be very careful with this type of pilot project at the moment. There is a lot of resistance, especially in the epidemiology community, toward having "some" health status data and "some" exposure data, and then having some people superimpose those two types of partial information and concluding that there is a cause and effect type of association between them.

Shostak: Right, right.

Wilson: So, we must be careful to guard against this kind of misuse of such information. There are a number of scientists, especially some

epidemiologists, who strongly oppose this type of misuse of data. They would rather not have such tracking at all, if the results are going to be misused in this way. Such misuse is an absolute "deal breaker." So, those of us who are interested in developing a national health status and exposure profile mapping capability need to take some "sensitivity training" on this issue of potential misuse. But, yes, you're right. This type of mapping represents a great opportunity.

Shostak: One of the things that was really interesting to me at the National Academy of Sciences committee meetings is the ways in which you're essentially preparing markets for the knowledge produced by the NIEHS. What are your models, if any, for that kind of stakeholder education and enrollment?

Wilson: Well, I don't know about models. There must be some. But, on the other hand, it is obvious that if the science of Toxicogenomics gets out ahead of the industry or the policy making community or other communities, then this could have a very negative backlash effect. So, in thinking about this NAS/NRC activity (Standing Committee on Emerging Issues), I'm not thinking so much about following a model, i.e., trying to replicate a model, but instead it is simply quite obvious that we need to deal with the issue. This is not a situation where I myself can understand, know, or predict the concerns. But, the Institute has created a way to have a dialogue and debate and for the toxicology field to listen to all

stakeholders. We will be able to work collectively, as a group, to identify what the concerns are and find out how far we can go with this new science and still have consensus. So, it will be wonderful if the new area of Toxicogenomics can make use of this NAS/NRC Committee to provide this kind of dialogue and to develop this type of information. The activity also will let the industry and other stakeholders know that the public scientific community is not running amok with the new Toxicogenomics approaches, but instead is being deliberate, and careful, and is listening. The stakeholders will learn that, "we can work with them and have input and have our needs and concerns appreciated." So that is one idea regarding the role of this NAS/NRC Committee. I suppose there is a model I could discuss. It is the Asilomar conference on recombinant DNA in 1975. You've probably heard about it. This was a case where, proactively, the scientific community made it known that there was a need to have more dialogue on the issue of safety surrounding recombinant DNA research. There was the notion that more process was needed, along with a more systematic way of going about assessing concerns. The issue of recombinant DNA safety concerns at that time was not as clear-cut to me, as is this issue today of the potential inappropriate uses of toxicogenomics.

Shostak: In what way?

Wilson: Well, the concern that use of recombinant DNA technology would pose a

human health hazard… I did not view this possibility as a significant concern at the time. But, many scientists had sufficient concerns so that the workshop at Asilomar was justified, and the activities that emerged from the workshop helped enable the field of recombinant DNA technology as we know it today, i.e., the Recombinant DNA Committees at institutions across the country and functions like that emerged directly from the Asilomar meeting. So, I hope that eventually, by fostering this activity with the National Academy/NRC, we can move toward a type of "responsible-use practice" for toxicogenomics that the scientific community can buy into as effectively as it has embraced the Recombinant DNA Committees around the country for making use of of recombinant DNA technology, or the current ethics committees around the country for dealing with ethical issues. Why can't we do the same thing with new toxicogenomics-based tests or procedures that might be damaging for product development? So, I would like the industry to buy into the idea of making use of this NAS/NRC Emerging Issues Committee in a robust way.

Shostak: Do you see signs of that happening yet?

Wilson: They are involved. And, they're very pleased that the this Committee has been formed, but they're sort of watching from the sidelines at the moment, probably wondering, "are they really serious about this activity, and will there be any examples of real benefit that will come out of it, like

a safe-harbor practices, or way to foster validation for new assays?" If the Committee can show some real products that the stakeholders can appreciate and buy into, then I think this will reinforce the idea behind the importance of this type of NAS committee activity. But, the fact that we are having those meetings -- you know, this National Academy Committee activity-- is a big step forward toward getting buy-in from the industry and other stakeholders and letting them know that we, i.e., the public scientific community, would like to work in partnership with them on making use of Toxicogenomics. So, I'm excited about what NIEHS is doing with this activity.

Shostak: It was fascinating. I really enjoyed being there, listening to it.

Wilson: Yes, I like the idea of building concensus in this way. We will see how we do with the activity over time. Now, of course, the "proof is always in the pudding" as to reducing to practice some of these general ideas and goals, but the fact that the Standing Committee has gotten this far is nice and very exciting.

Shostak: And it sounds like the mechanisms are already in place to go further...

Wilson: Yes.

Shostak: In that here's another committee being formed that would be a study committee.

Wilson: Right, the "study committee" you are referring to is different from the Standing Committee and will be able to write a standard NAS Report.

This type of NAS Report is a big deal, and it will be most useful. And yes, that is one big step forward. But, we need to take other steps too. We certainly need to take other steps, and we need to be able to fund the Standing Committee's activities over time. That is not trivial. It costs a lot of money to maintain one of these NAS Standing Committees. And, the various spin-off activities also can cost a lot. Every time the Standing Committee gets a new idea, well, you know, that's another possible [expense]. And the agencies have to bear most of the burden of funding these activities. So, this funding topic represents an interesting administrative challenge, and there also is a cost in terms of our effort toward defending the activities. That is part of "the heat in the kitchen" associated with a job like this one that I have here at NIEHS. One must be able to defend these activities and interpret them, and the activities must be productive. One must be able to evaluate and to show productivity.

Shostak: You're defending them to Congress?

Wilson: No, to each sector or part of our constituency, like to the rest of the NIH, to the Institute's National Advisory Council, to the extramural community, to the NIEHS staff, and so on. You have to get buy-in on these activities, and all of this doesn't just happen like "poof," you know, like magic. It takes a lot of work to be able to support this NAS Committee activity, not to mention the task of working with the Committee itself to help foster productive outcomes.

Shostak: Let me switch gears a bit and ask you about the research agenda moving forward in your laboratory at this time. And I'm asking in particular because something I read in your CV made me aware that you have used genetically modified models as part of your research, and I'd like to know more about that.

Wilson: Yes. Well, in my own lab, our core scientific expertise is a sub-field of biochemistry called enzyme kinetics. It is the science of how enzymes work, what causes them to work at different speeds. Enzymes are the machines in our cells that are responsible for accelerating the vast number of chemicals reactions that are necessary for life. And so, we got the idea about 20 years ago now, regarding one of the enzymes we study at the present time, that we could do structural biology with this enzyme. We found that we could prepare a ton of the enzyme in purified form. And so, having been trained originally in chemistry and physical biochemistry, I thought, "boy (!)," wouldn't it be exciting to be able to understand this enzyme, at the level of its chemical reaction (DNA synthesis), and that the use of structural biology would be the pathway for achieving this goal. We started the project at that point by strategically attempting to understand in exquisite detail how this enzyme (DNA polymerase ß) functions. A factor in this decision to take on the project was the hunch that the enzyme plays a role inside the cell of DNA repair. . .But that wasn't the driver… The real driver was my interest in understanding how the enzyme manages to

achieve catalysis during DNA synthesis. And over the years since that decision to conduct the project, we've been successful at using the approach of structural biology to leanhow the enzyme functions. In other words, that is the crystal structure right there [poster on the wall]. This is an image of the cover of a journal in the field for biochemistry. An article describing the discovery of the structure of the enzyme was published in this journal (Biochemistry). We make use of that kind of information to be able to understand questions about how the enzyme functions or accomplishes its job in the cell.

Shostak: I'm smiling because I know you're looking at that and understanding what it means, but ??….

Wilson: Well, see those ribbons? They illustrate DNA, and the enzyme is shown bound to DNA just at the instant before DNA synthesis occurrs and . . .

Shostak: I recognize the helix.

Wilson: Yes, and the DNA helix is helping with DNA repair mediated by the enzyme. And so, moving on with my story, a few years after we started the project, I said to myself,, "Okay, this project is probably going to work, but it is going to take a very long time, and in order to sustain the project for the period of time necessary (to understand the enzymes' mechanism), you need to have a good, solid biological underpinning and a public health significance: You need to know for sure that the enzyme has a role in DNA repair and that DNA repair is important for human

health." And so, we started doing animal model studies at that time, to try to nail down the cellular role for the enzyme. This was more to fulfill a strategic need, rather than to meet a burning interest, you know, in what the biological role is. We have continued to do experiments over the years focused on understanding the biology of the enzyme (DNA polymerase ß). During the initial process of learning how to do those biological experiments, I did a lot of reading and studying on the topic of DNA repair. I wanted to know or grasp the question, "How does DNA repair work?" I guess that's probably what you're driving at with your question, "How is it that deficiencies in DNA repair can make human beings more or less susceptible to environmental exposures?" The DNA repair field is an area where there are a lot of good examples of this issue of human health significance. Indeed, in the area of susceptibility, individual susceptibility, DNA repair is a big gorilla, along with metabolism enzymes. So, this was a summary, just a little bit of the background information, that makes it easy for one to understand some of these broader concepts of genetic susceptibility and so forth. In the lab, we're working on the same topic, but in a more focused way, toward understanding the mechanisms of how cells deal with chemical toxicants (chemical stress) or radiation stress. A big part of the coping strategy involves DNA repair itself. But, another big part, equally important, is the signaling that goes on inside the cell once the genomic DNA becomes

damaged. The cell immediately detects the fact that damage has occurred and then signals to the rest of its machinery, to stop the cell division process. In other words, the cell says to itself, “there is a bad thing happening here with my DNA; let’s just put a hold on everything, until we see if we can fix this DNA damage.” This signaling system is of great importance to a cell and is becoming a main research interest for us. We just kind of stumbled into it. We were just following our noses. One of the DNA repair enzymes we had been studying for a while just happens to be a signaling factor, also. And so, we got interested in signaling and started doing assays with cells, where we could observe that this type of DNA damage signaling was happening. Initially, we were amazed at the strength of the signaling response; it was like, “holy smoke, look at that signaling!” We found that the signaling is related to DNA repair, and we wanted to understand how this relationship was happening. For example, when we genetically engineer cells to be deficient in DNA repair, then they signal to put on the brakes for cell division, but they don’t recover from this signal and eventually die. On the other hand, a normal cell will signal, but then, it will repair the damage and eventually release the brake and continue to divide. This type of cell signaling process is really fascinating, and we are trying to understand it at the molecular level. Our lab, just as I alluded to a few minutes ago, is very multidisciplinary. We’re doing crystal structures of DNA repair enzymes, cell and molecular

biology of repair, mouse genetics, and enzymology of pol ß, and all of this relates to, or is focused on, this question of the cellular response to chemical toxicants or radiation. So that, in a nutshell, is what we're doing in the lab.

Shostak: That's great. Thank you for explaining that.

Wilson: I think my research program is related, in a general fashion to a number of the broader topics NIEHS is involved in. Many features surrounding the scientic approaches are similar. For example, during my career the use of genetics has been a huge factor. When I was a student, I was in a department that emphasized genetics. All the research groups in the department were working on some form of bacterial genetics or viral genetics, and that background has been fundamental for me, just as the use of genetics is absolutely fundamental to the whole field of biomedical research. I've never been a research geneticist, per se, but have always appreciated and observed how powerful this approach is.One can study a phenotype in a cell system where one has no clue, as to what the cellular requirements are for this phenotype. One can mutagenize the cell's genome and observe how the phenotype changes; you can see from the way the altered cell responds that something has happened regarding the phenotype. So, this in essence, is what genetics is all about. You know, in using genetics one works with the entire "black-box" cellular system and asks about the dissection of requirements within that living system. This

was the classical, workhorse approach that many scientists used during the 50s, 60s and 70s and still use to an extent today. But today, with all these new molecular techniques, there are new approaches to discovery about requirements for a phenotype, where one is not forced to use straightforward genetics.

Shostak: And that includes systems biology?

Wilson: Yes, systems biology, possibly. This is a term describing the idea of understanding macromolecular interactions in a cell in the framework of a complete engineering diagram or network. This is basically what "Systems Biology" is, where the whole universe within a cell would respond to a stimulus in a certain way, and one would hope to be able to calculate what the response will be, in essence to predict the response. But, the idea of being able to do this is just that at the moment, "an idea." Reduction to practice is so far in the future that it is hard to know what this type of approach will actually look like once it is achieved. But, with classic genetics, you can go in the lab tomorrow and use genetics to figure out new requirements for a cellular response. You know, lets assume that taking both of my thumbs apart and into these positions is the response or phenotype one wishes to analyze. Then, one can mutagenize the system and find cases where the response doesn't happen, or just one thumb goes into position. You will not be able to understand why this change occurred, but you can conclude that the new mutant cell is deficient in the

response. Genetics allows one to find the number of requirements or genes necessary for a cellular phenotype, because if you mutagenize a cell exhaustively, thousands of times, and you end up finding the same cellular requirements -- let's say this one, that one, and that one, but no others – then you have discovered that there are three main requirements (genes) for the phenotype in question. Then, one can drill down using molecular biology techniques and find out the molecular mechanism of this mutation effect. But, on the systems biology scale, it is not a question of three different requirements or genes that you would be looking at. It is a question of understanding a network of hundreds or thousands of genes or gene products and of how subtle changes in the overall cellular network can change cellular behavior. This extraordinary complexity is the reason that we still need to use classical genetics in understanding toxicant responses; we know so very little about the cell's networks that we still need to work at the classical genetics level, just to define the minimal requirements or genes involved in responses. This viewpoint or philosophy is one reason why we need the Mouse Consortium program (i.e., the CMGCC) and other types of mouse genetics experimentation: to define the basic molecular requirements for responses to toxicants.

Shostak: We're at the end of all of my questions for you, which is a remarkable thing. However, I did want to raise the question of how you think about the uses of historical research, like what I'm doing, from the perspective

of the Institute.

Wilson: Well, I think this approach/idea of publishing an article is incredibly useful. And why? Because the information you are collecting on perspective, philosophy, and outlook of senior leaders needs to be shared. The information needs to be shared with the broad community, at the moment, to help us all understand the issues, the pros and cons of scientific initiatives, and the information gaps, and the information will allow us to be able to achieve consensus faster. And so, I would refer to the article as a type of "thought piece." This is what you're talking about doing, and also of lacing the article with history as a framework. But, it is really a "thought piece." Scientists are just so thirsty for that kind of material, because they spend a lot of time thinking about strategies and answers to questions like, "where is this field going?", or "what new techniques can I use?", or "what new interpretations can I put on this data?" So, it is this idea of doing a "thought piece" that I find so interesting, and I think you could make a significant contribution here toward helping us gain consensus. Actually, I think this article is a "no-brainer" with regard to providing a service. But it does put the finger on..

Shostak: On me.

Wilson: On you, yes. Right. and, there are a lot of places to publish this kind of article, and especially in our field journals like *EHP* and similar great places, and NIEHS has a journal now on toxicogenomics. That's another

one. And, of course, there are all these broader, more general journals that are appropriate.

Shostak: But I really appreciate you reminding me that I shouldn't be thinking just about the history-of-science kinds of journals, that for this to be useful to more people it needs to appear in journals that are the primary sources for the field.

Wilson: Right, exactly right.

Shostak: Okay.

Wilson: You don't need to restrict publishing in just one place, either.

Shostak: Right. I can speak the language of my colleagues in history in one piece and publish it elsewhere as well.

Wilson: Yes, right. I guess the bottom line is that I don't think a lot of these points we covered today concerning new programs or initiatives, as you can see from earlier in this conversation, are surprising or unique or novel. This is really not the case, and that perspective is interesting in and of itself. This is the way I view many of the initiatives we are fostering here at NIEHS at the moment. Other NIH institutes and federal agencies are conducting new initiatives that make use of the latest technologies and approaches, as well.

Shostak: Do you see that as true for toxicogenomics as for other initiatives we've talked about?

Wilson: I think it's true for all of these initiatives we have talked about.

Shostak: Because in the conversations I've had with people who've been involved

in developing toxicogenomics at this institute, there is a real sense of, "we named this field, we developed the first tools for this field…"

Wilson: Well, this is correct about Toxicogenomics, per se, regarding the discipline of toxicology. But, if you consider the situation with a more general view, you know, a jet-airplane view, we are talking here about global genomics, about messenger RNA quantification, protein quantification, informatics, and all of these "omics" topics that have come from a much broader research community than toxicology. These have just been sort of taken from this broader activity and applied here in the area (toxicology) that these folks are thinking about. But, it's not true that these things grew up out of our field of toxicology. They really didn't. I mean, this was something that happened within a much broader enterprise. We are applying the "omics" approaches in toxicology, which is good and interesting. That's my take on it.

Shostak: What's interesting to me about that is that it's clear that the technology was developed outside the field and then brought to and fostered for applications in toxicology. But now is the application of the technology in toxicology is starting to cause transformations in what it means to do toxicology?

Wilson: Yes.

Shostak: So that, for example, people talk about spending more time at the computer than at the bench, working in big multidisciplinary groups and

looking at mechanisms rather than the kill them and count them approach? So, at the same time that I take your point that it comes from the broader field of science, it seems like it nevertheless makes targeted transformations . . .

Wilson: It does.

Shostak: . . . in this science.

Wilson: Absolutely, right. There's no doubt about that.

Shostak: Okay. Because I've been thinking about this and writing about it, it's confirming to me to hear you say that.

Wilson: I think that is true. But, the same point is true of other fields as well. So, is it a statement about toxicology, or is it a statement about the evolution of biomedical research in general? Let's consider the practice of "cloning by phoning." This used to be what people often did in the 1990s; if one needed a cDNA, one often did not clone it; instead, one picked up the phone and called around and eventually obtained it through the mail. And then, there was a phase where one didn't even bother to clone by phone. You would just do a PCR in your own lab, because one could look up in a database and find out how to select the primers and conditions for amplification from a routine preparation of messenger RNA. Well, nowadays, we often don't even clone a cDNA anymore, to find out what the function of the gene product is. One uses a computer and lines-up sequences, and compares sequences of related cDNAs, and looks at the

sequence of the cDNA of interest in all the other species, and everything; and then, one does these predictions about the structure and function of the gene product without doing any wet lab experiments. So, in many cases, one doesn't really need to clone anymore. It's amazing. But, everybody's doing this. It's not just in the area of toxicology. So, it's just amazing how enterprise-wide we're using all these technologies and ways of thinking about problems that are so very different from practices several years ago. Now, it would be a big problem if the field of toxicology either did not use or stopped using these new approaches.

Shostak: I was just going to ask you that.

Wilson: Yes. And avoiding that scenario is not a given. In science, entire fields and individual investigators must always keep struggling to stay current, and wondering about the question, "Well, will something new work?" And, some approaches will have to be dropped, things that one can't even imagine giving up on. One must be open to the notion that "Maybe there is something out there that is more exciting, even more so than this work I can't even imagine giving up on." And, one learns to pay attention to this notion over time. By trying new things and then observing that, holy smoke, this is actually better than the former way," (which one still loves and can hardly even think of parting with it). And so, scientific fields like toxicology need to promote that kind of thinking, to foster the new, more vigorous types of approaches to the time-honored problems, and that is

good. The initiative in Toxicogenomics in the field of toxicology, or similar new initiatives in the other fields, is promoting the evolution of new approaches and better technologies, and that is good for any field, and it will reap tremendous benefits. So, that concept is an important point. It doesn't always work this way in fields or areas of research. There are fields where the approaches, technologies, and ways of thinking are still stuck in the same 1950s, 1960s, 1970s ways of doing science. Yet, at the same time, it isn't special to the field of toxicology that all of these exciting new approaches and opportunities are happening. NIEHS does have to make an effort to grasp the status of what is going on, enterprise-wide, in toxicology and then to foster application of these new approaches in toxicology. This does take an effort. You do have to define what the new stuff is, and then get a grip on it, and build consensus. And, of course, some sectors of the field lag behind. For example, epidemiology is an area that is lagging behind right now in picking up these new molecular approaches, and some of the hazard assessment/policy areas are lagging behind, because of this conservative outlook situation we discussed earlier. The science is way out here… but they're still hung up on this conservative, validation point and other slow-moving perspectives like that.

Shostak: That's again, what makes the environmental health sciences, broadly construed, so sociologically interesting. You have this pressure,

enterprise-wide pressure, to keep up and be current and be doing things with the best, most innovative practices possible, and then you have the users of your science, who may or may not be . . .

Wilson: Yes, right, who want you to slow down.

Shostak: Right. Be willing to kind of go on that high-speed train.

Wilson: Oh, yes, exactly right, right. And so this is very interesting. But, both of those points are essentially a fundamental part of the field of toxicology. It is a lot of fun to understand these points and to try to get a grip on them, and to consider what they mean in terms of day-to-day practices and things like that. That is what makes it so much fun to work in this field. That was an interesting perspective you shared earlier about the view of scientists in the Toxicogenomics unit here at NIEHS who are taking "ownership" in creating that the toxicogenomics enterprise. It is gratifying that they feel this way. There is definitely something to be proud: The Institute has had a role in applying the "omics" revolution to toxicology. If we can demonstrate that it really works scientifically, Toxicogenomics will have a big impact on the way toxicology is done in the future.

Shostak: I look forward to seeing what happens, as you know.

Wilson: Yes.

Shostak: I'll turn this off.

END OF INTERVIEW