Environmental Components of Gene-Environment Studies
David A. Schwartz, M.D., M.P.H.

DR. TUCKSON: We are very happy that two experts are with us today to speak on this topic.

Dr. David Schwartz is the Director of NIH National Institute of Environmental Health Sciences and Dr. John Hewitt heads the Institute for Behavioral Genetics at the University of Colorado. Their biosketches are in your table folders.

Dr. Schwartz is joining us by video from North Carolina. His talk will help us to understand more about the environmental factors that would be a part of a large population project. He will help us to understand how those environmental factors are measured and what we are likely to learn from studying their interactions with genetic risk factors. He will also discuss some of the policy issues associated with measuring environmental exposure in a large scale study.

Dr. Hewitt will then focus on the social and behavioral factors in the environment and the way that these factors interact with genetic risks to affect health outcomes.

Dr. Schwartz, we really do appreciate your taking the effort and all of your people there at North Carolina who made it possible for the technology to work. With that, I would urge you to take yourself off mute and please share your thoughts on environmental components of gene-environment studies.

DR. SCHWARTZ: Thank you very much.

(Slide.)

It's a pleasure to be here with the committee. I want to thank the committee for making time for me on their busy schedule.

Let me first say that I'm highly supportive of the report of the committee and I'm appreciative of the fine work that the committee has done in this regard.

There are four issues that I'd like to address during the brief time that I have on your schedule. One is I'd like to clearly establish the need and the importance of precisely measuring environmental exposures when considering susceptibility for a variety of diseases.

Secondly, I'd like to be able to demonstrate how the exposure biology program within the Genes and Environment Initiative takes some very important steps to develop these very precise measures of exposure.

Third, to show how the work in the Genes and Environment Initiative, and specifically the exposure biology program, can interface with the grander plans that the committee put forward in terms of the population-based studies.

And then, lastly, just reflect on some policy issues that are relevant not only to genetics but also environmental concerns when considering etiology of disease.

So I can't control the slides from this end but if I could have the next slide.

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This next slide I took from a publication of Francis Collins where he demonstrates the clear importance of the sequencing of the human genome in terms of understanding biology, physiology and how that physiology relates to a more clear understanding of disease and the distribution of disease in populations.

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No, go back.

(Slide.)

So the importance—well, it doesn't much matter but the issue is that our belief—a belief that Francis and I both share—is that focusing on environmental exposures when considering genetic risk factors are a way of accelerating those discoveries, both the basic discoveries, as they relate to basic biology and pathophysiology, but also maybe more importantly in terms of etiology of disease.

Let me give you two reasons to consider environment when considering the etiology of complex human diseases. In an editorial, Walt Willett commented on the importance of environmental factors and behavioral factors in terms of the risk of developing many of the complex diseases that are faced by Americans and people all over the world.

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And basically what he illustrates in this slide is that between 70 and 90 percent of the etiology of major diseases in the United States are caused by reversible behaviors and exposures and in considering the etiology of these complex human diseases, less than five percent of the etiology of any one of these complex diseases, colon cancer, stroke, heart disease and diabetes are caused by single gene mutations underscoring the importance of considering environmental exposures.

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We've been looking at twin studies very carefully and basically what we have found is that when you look at many of the complex human diseases, such as asthma, diabetes, prostate cancer, breast cancer and Alzheimer's diseases, diseases where there are several—at least several twin studies to rely on, between 20 and 50 percent of the etiology of any of these diseases is caused by factors other than genetic factors. Largely being environmental factors, behavioral factors or nutritional factors that are critical in terms of the development of these very important disease processes.

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A second reason for considering environment in terms of understanding the etiology of disease is because environment can simplify the phenotype of these complex human diseases. For instance, in asthma the studies of generalized forms of asthma have demonstrated a genetic etiology of asthma. However, when you look at the loci throughout the genome or the genes that have been associated with the development of asthma, almost every single chromosome has a location on it that is associated with the risk of developing asthma.

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However, this is no real surprise when you consider the fact that multiple exposures account for the etiology of asthma and that asthma is a very complex biological process, and there are many phenotypes of asthma from the development of air flow obstruction to wheezing to the requirement of medications for the treatment of asthma.

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Now our belief is that if you break down asthma by etiologic variance and consider that house dust mite induced asthma—

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--is probably very different than ozone induced asthma, is different than endotoxin induced asthma—

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--you can use these environmental exposures as a way of creating a very narrow pathophysiologic phenotype that can then facilitate understanding the genes and the biology that underlie those important disease processes. In fact, this approach has been very successful in understanding specific aspects of human biology of disease pathogenesis, individual susceptibility, impact on prognosis and treatment, and also the distribution of disease in populations.

(Slide.)

Now with the support of Secretary Leavitt, Dr. Zerhouni, the other institute directors, Francis Collins and I developed a Genes and Environment Initiative. The basic approach in the Genes and Environment Initiative is to use genetic variation and also environmental variation as a way of understanding the etiology of complex human diseases and to focus that on understanding diseases of important public health import. So the idea is to not only do whole genome association studies but combine those whole genome association studies with much more precise measures of exposure as a way of looking at the combined risk factors—these combined risk factors for the development of these complex human diseases.

(Slide.)

When you consider the precision of being able to measure genetic variation from one individual to the next and you compare that to what we're currently able to measure in terms of environmental history from one individual to the next or exposure history from one individual to the next, it's patently obvious that we need much more precise measures of exposure. So within the Genes and Environment Initiative we have developed an exposure biology program to do precisely that, which is to develop measures of exposure that reflect biological responses to classes of toxins or to measure biological responses to nutritional changes or activity levels that provide us with a much more precise estimate of the risk of going on to develop disease, and then to be able to measure the association between that risk and the genetic factors that place one at risk of developing disease.

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So then the idea is to--

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--is to develop these personalized biological measures of exposure that provide a level of precision that allows us to look at both genetic variation and environmental exposures in combination in terms of the risk of developing these diseases.

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One of the examples that I'd really like to focus on is that of hepatocellular carcinoma.

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We've known for many years that hepatitis B virus through the development of hepatitis and hepatic cirrhosis place individuals at risk of developing hepatocellular carcinoma.

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It has been recently appreciated by Jerry Wogan and John Groopman that exposure to aflatoxin through aspergillus flavus, a common spore that contaminates food especially in Southeast Asia, also places individuals at risk of developing hepatitis and also hepatocellular carcinoma.

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But it wasn't until they identified, and others identified, biomarkers of exposure to both hepatitis virus and also aflatoxin.

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And they relied on two specific biomarkers that they were able to then identify the relative risk--

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--of developing hepatocellular carcinoma that was contributed both by aflatoxin and hepatitis B, and also that they were able to appreciate the synergy between these two factors.

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One important issue is that if they went back to dietary history and they looked to see whether dietary exposure to aflatoxin was associated with the risk of developing hepatocellular carcinoma, they weren't able to identify a relationship here. This clearly demonstrates the importance of these biomarkers in terms of the risk of developing disease and demonstrates the importance of these biomarkers in terms of understanding how the dietary factor like aflatoxin contributes to the risk of developing disease. Something that they wouldn't have appreciated had they relied simply on dietary history.

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Another important factor is that it took them between 25 and 30 years to develop the epidemiologic evidence, the populations, the biomarkers and then to test those biomarkers in populations before they were able to come up with this association and go on to develop preventive strategies in terms of preventing the development of hepatocellular carcinoma.

We believe through the Genes and Environment Initiative we'll be able to compress this time line so that we'll be able to identify the etiology of disease within a five year horizon.

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What can we currently measure? There are very important exposures in the environment that place individuals at risk of developing disease, polyaromatic hydrocarbons that are released by smoke and various forms of air pollution, particulates in the air, dietary factors and physical activity factors that we currently measure by questionnaire, monitoring of these substances in the blood, urine and air samples, as well as measuring these substances in DNA adducts and protein adducts.

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Next.

(Slide.)

This allows us to then see whether these factors are associated with a risk of developing various diseases of public health import.

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The problem is that this approach makes it very difficult to understand the mechanisms that underlie this association and this approach ends up being a poor predictive factor in terms of disease pathogenesis and progression.

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So the limitations of the current exposure data are that they rely heavily on questionnaire information and environmental assessments, not personal assessments. They lack sensitivity and specificity. They are qualitative and not quantitative, and they lack precision in a measurement assessment. They are environmental, not personal in terms of their exposure measurements in exposure assessment. And they don't address a contribution of diet or lifestyle in a quantitative fashion.

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In aggregate, what happens is this limits the power to make definitive conclusions about relationships between exposure and genes as well as these two risk factors and the development of human diseases.

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So then we think through the Genes and Environment Initiative that we'll be able to have a greater impact in terms of understanding the biological importance of this.

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By measuring the biological impact and developing indices that allow us to measure the biological impact and assess genetic susceptibility.

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In aggregate, what will happen is this will allow us to develop mechanistic linkages that are better predictors of disease risk.

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So there are two aspects to the exposure biology program within the Genes and Environment Initiative. One is the development of new technology, which we believe will take at least a four year period of time. A second is to adapt existing technologies to various exposures that are clearly important in terms of the risk of developing disease. We think we're going to be able to develop assessments of exposure that are personalized assessments of exposure but also assessments of exposure that tell us whether someone is biologically responding to those exposures. We believe that that's within the horizon of the Genes and Environment Initiative.

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And we think that these exposure assessments will allow us to have tools that will be available to studies such as the large population based study supported by the Secretary's advisory committee but we think that these tools will also be accessible to other studies, case control and cohort studies that are interested in examining the importance of diet, nutrition--nutrition, diet, physical activity as well as a variety of environmental exposures.

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The policy considerations as they relate to environmental assessment are very similar to the policy considerations as they relate to genetic assessment because they address very similar issues that relate to privacy and confidentiality of data, and these are things that we need to seriously consider and figure out how to deal with in terms of protecting the privacy of our study subjects.

We need to foster public involvement in these studies both before, during and after the study and we need to keep in touch with the study subjects in a very clear way. We need to develop consensus policies for data access and sharing as well as public and private dissemination of the data and communication of the important study issues as they develop and as they come to fruition.

A very important issue related to these exposure assessments is we need to assess how the public is going to respond to these exposure assessments before we get involved in the very large population based study looking and examining the risks of environmental exposures in terms of the risks of developing various diseases.

So those are the comments that I wanted to make and I'll stay on the line for the question and answer period.

MS. CARR: Thank you, Dr. Schwartz. This is Sarah Carr. I'm the Executive Secretary of the committee and Dr. Tuckson, our chair, just stepped out for a moment. As you indicated, we're going to have the Q&A and we appreciate your staying on.

So we'll turn now to John Hewitt for a presentation that will focus on the social and behavioral components, and hopefully will complement Dr. Schwartz's presentation.