Capturing Complexity: The Scientific, Societal and Ethical Meanings of "Environment" in Genetic Research
May 9, 2008

Panel 4 Speakers (in order of appearance)
Hank Greely (HG)
Paul Wise (PW)
Richard Sharp (RS)
Sara Shostak (SS)
Audience Question (AQ)
Ruth Ottman (RO)

Introductory Remarks

HG: Again three speakers. The first is Paul Wise from Stanford's Department of Pediatrics. The second is Richard Sharp from the Center for Bioethics at the Cleveland Clinic. And the third is Sara Shostak from the Department of Sociology at Brandeis University. So Paul.

Panel 4
The Policy Requirements of Gene-Environment Research

PW: *(Slide 1)* Well my job is to make policy sense of what's been discussed so far through the course of the day. *(Slide 2)* And what I would like to do is basically review quickly how policy is made just so we're on the same wavelength. The first thing in terms of policy formation is generally considered objective analysis. You get publication, and then it turns into policy. Well of course in the real world, that never happens. As Tony Soprano would say, "Forget about it." And in fact what you see in the real world, the relationship between science, particularly developmental science, and policy is in fact a dance that takes place between the scientific literature, the new scientific insights, and the requirements, the preoccupations of society at large.

(Slide 3) When you go back to the turn of the twentieth century, and you look at the early developing science of child development, and how it fed and responded to the growing societal concern with urbanization and the plight of children in a variety of deleterious social settings. And in fact this science and its interactions with the requirements of the society at this time meant really for the first time in American history that child development was in state interest at all and lead to a whole series of progressive reforms in that period. And also child development, developmental science interacted heavily in the 1960s and fed and responded to the call of civil rights and questions of social justice and began to reframe child development in fact as equal opportunity and generated a whole series of public reforms, policy impulses, such things as Head Start didn't get its name by accident, in fact was part of the Office of Economic Opportunity in its beginning days. More recently, the science of development has become in many ways more personal because the science of human development has begun increasingly to break down the

traditional boundaries between normal and abnormal, and we cast human development as a series or a spectrum of individual capacities and challenges. And what has happened is that in fact perceptions of human development have become intertwined with perceptions of self, of identity.

(Slide 4, 5) And what you have seen in the popular culture, the popularization of human, particularly child development, based on personal memoirs of early life tragedies, early life traumas, that somehow influence who we are as adults and *[sic]* has captured the public imagination in many important ways. And I have just a few of these memoirs that have been perennial best-sellers including *A Million Little Pieces*, which for the publishers turned into *A Million Little Rebates* because *(Slide 6)*, the second time Oprah's on the slide here, it was shown to be largely a fake. And in fact there have been a series of memoirs about early life traumas that have turned out to be fakes, both in terms of Holocaust literature as well as others similar to here. That increasingly perceptions of child development have been intertwined with self-perception, and there has been a dramatic shift from concern about social improvement to self-improvement. That in fact what you get are these stories, these memoirs, reading like Horatio Alger's stories for *Prozac Nation*. And in fact if Dickens were writing *A Christmas Story [sic]* now, Tiny Tim would be off crutches and have ADHD. So the argument basically is that public policy is always profoundly interactive with societal requirements, ideology and perceptions of public need.

(Slide 7) Now we could look at policy a million different ways. This is a model that has been developed and been used, I think fairly successfully, by two of my mentors, Julie Richman and Leon Eisenberg, which suggests that really you've got a knowledge base, the science if you will, not only ideologic *[sic]* science base but the development of knowledge that would in fact enhance the capacity to intervene and efficacy knowledge base as well. But that alone has very little influence on policy without a social strategy. There needs to be social mechanisms of *implementing* what the knowledge base is providing, that if we think of policy as the transformation of societal intent into societal action, it requires some notion of effective social strategy. And of course what we always talk about is the political will to act on those social strategies, to act in fact on the right relationship between knowledge and public policy.

(Slide 7) So when we begin to think about these kinds of issues and bringing it back to the science we're discussing today, it's really quite impressive of how historic, in my view, the impact of gene-environment interaction, but what I would suggest is far more relevant and likely to be more important is gene-environment interdependence, on policy insights. One is something that Atul and some of the prior speakers have talked about *(Slide 8)* is what in fact is going to happen to the traditional taxonomy of disease, particularly the disease-policy taxonomy, when you have insights into these gene-environment interdependence precursor conditions. And what is likely to happen is the re-definition of our understanding in the policy world of disease formation, but also of disease categorization based on a whole set of really thousands of new, multiple gene-environment precursor conditions. *(Slide 9)* What is you get in fact is these kinds of precursor arrays rather than one or two or three disease categories.

(Slide 10) Now what are the implications? Well the first is that we're going to be talking a lot more about the identification of, it could be people see it as genetic profiling in a way, but in my mind particularly after the conversation today I'm more convinced, that when we talk about genetic profiling we're really using it as proxies for gene-environment clusters of some sort.

And that what we get is some sort of personalized medicine, where you have notions of gene-environment precursor conditions becoming the root content, the root substrate, for clinical intervention. And what you see of course is now a whole array of precursor conditions being identified that weren't being identified earlier. And for a pediatrician, all of this is heading directly into the pediatric world. We saw direct-to-consumer marketing of genetic screens for a whole bunch of different candidate predispositions for suspected candidates for disease states. That was in a *New York Times* article, and the reporter had direct-to-consumer genome screen done, and she explained how great it was and how she understood why didn't like Brussels sprouts and other things, but at the very end of the session she said, "I'm going to go out and have this done for my five-year-old." In other words, why wait until you're forty-five before you get your genome screened? The pressure will be to bring all of this capacity into earlier and earlier periods of life. In fact, newborn screening is not going to look, in my view, anything like it looks now; it's going to be far more chaotic, and particularly with direct-to-consumer genetic screening going from a thousand dollars to a hundred dollars and the candidates that are going to be screened are going to be far more numerous is that basically you're going to have personalized medicine in the neonatal period.

(Slide 11) Now it also raises real questions with other things happening in medicine that are of direct policy concern. There has been a lot of pressure to improve quality in health care by standardizing health care. Practice guidelines, checklists, get discretion out of the patient-doctor encounter. Well that's colliding directly with individualized care based on arrays of identified, personalized risk. How we negotiate that territory has not been even considered except by people like Atul and some people who work on quality improvement because this clash is going to be significant.

The other issue is important when we talk about social strategies, that over time this has generally been viewed as collective social strategies, and now we're talking about personal social strategies. What is it going to do to collective action in the policy arena to have this kind of splintered epidemiology of risk? It's also unclear to me how that's going to play out.

(Slide 12) The second area was discussed earlier by Dr. Schaffner, particularly in presentation of Caspi's group's work, is norms of reactions *(Slide 13)* where we recognize that the phenotypic expression of different genotypes will vary over different environments. And in fact, what is not only interesting that things will cross over, but in the policy realm, it doesn't have to cross over to be of particular interest because it could be trivial in certain areas and then important in other areas of environmental expression. And the notion of norms of reaction basically breaks apart our traditional ideas of protective and harmful exposures *(Slide 14)* where in fact you get residents in the policy arena for things like this, and in fact *(Slide 15)* the notion of preconditioning in boot camp for preparing people to deal with combat of course is now being brought into the whole arena of life course arena *[sic]*. *(Back to Slide 12)* And in fact the arguments that this could be developmentally confined. *(Slide 16)* In other words that you have things taking place early in life that will in fact influence directly your health trajectories over a lifetime, that you sort of get a cannonball shot taking place because of things taking place genetically, epigenetically, whatever early in life that will define things later on. But when you look more closely of course, the cannonball doesn't particularly look like a cannonball, it looks more like a whiffle ball because you get punctuated things taking place in life. As a kid, your

parents die and your pets die. People start smoking, people stop smoking. And these things will be highly interactive and gene-environment interdependence, I feel, is likely to be far more complex than these kinds of life course trajectories would imply.

(Slide 17) Now what are the policy challenges? One is that we need to combat a splintered epidemiology in the policy world. We need to begin to re-aggregate these gene-environment interdependence clusters, if you will, in ways that makes sense for policy, that are formatted directly for policy, and working with Atul and others to come up with reclassifications, re-aggregations, that in fact facilitate constructive policy. A second is to recognize that for policy the amenability of intervention is always key, and there's nothing about gene-environment interdependence, either taking place early in life or later in life, that precludes its amenability for change later on life. There are many illustrations of things that have social, genetic interactions early in life that have very powerful social influences, powerful genetic influences, whole streams of cascades of interaction, but because you have a highly efficacious intervention, virtually *all* differential outcomes are based on differential access to that efficacious intervention. And the last of course is frameworks, frameworks for collective action. Frameworks are important. Frameworks are metaphors, and metaphors are tools. Like language, metaphors, frameworks are instrumental; they have meaning only to the extent that they move us to collective action. Merely using frameworks to depict empirical relationships is insufficient because what is required for public action, in this environment as in any other, will be solidarity, collective action. And solidarity is never discovered; it's created. What we're going to need is a response to this wonderful new science that provides us with the imagination to create the new language, the new frameworks, the new metaphors and sometimes the new poetry that will show us the way. Thank you.

Disease Advocacy and Contested Environments

RS: So like everyone, I think I'm struggling with this issue of how to find a balance between saying something interesting and saying it very, very shortly, briefly. And so what I did is I took the easy road and actually wrote out my comments; no Power Point for me either so my apologies for those of you who have a hard time following the argument given the fact that it's written out here.

But my arguments on going to focus on how public health advocates are interested in shaping concepts of the environment as they relate to studies of gene-environment interactions. Since I was asked to present, I believe in part because I worked on a project called the Environmental Genome Project, I'm going to frame my remarks in the context of some personal experiences that I had while working at the NIH on that specific project.

So the Environmental Genome Project was among the first of what we might think of as a second-generation genome project. The second-generation genome projects followed in the wake of the main Human Genome Project and were made possible by the genomic data and the sequencing tools that were produced. In the case of the Environmental Genome Project, the aim was to establish a genomic database that environmental health researchers would then use to begin deciphering genetic contributions to environmental response, to occupational and

environmentally mediated diseases. So the Environmental Genome Project was initially conceptualized as what we might call a genetic re-sequencing project in which roughly five hundred genes that were known to play some role in environmental response would be re-sequenced for the purpose of chronicling single nucleotide polymorphisms that existed in those genes. Those SNPs would then be made publicly available through a public database like dbSNP with the hope being that environmental epidemiologists and other public health researchers would use those data to design population based studies that would examine genetic contributions to these environmentally associated diseases.

I was hired as the staff ethicist for the Environmental Genome Project in October of 1997, now over ten years ago; it seems like it was just a few days ago actually, but it's been quite a while now actually. And my charge when…I was hired there as a graduate student, just so you know. Don't think I'm sixty-five years old or anything; I was only ten when I started there. My charge when I was hired there was three-fold. I was asked to identify key ethical issues that were associated with the project, to write a series of white papers that would frame these ethical issues and propose policy issues for responding to those. Really something actually if I would have been able to do that. And third, to help the leadership at the NIH to think through the need for an ELSI-type program. Those of you in the audience, many of you in the audience may be familiar with the Ethical, Legal and Social Implications program that grew up around the Human Genome Project in which approximately five percent of the total budget of the Human Genome Project was set aside for these types of social studies. Lots of folks, since it's been eighteen years more or less since that program has been announced, are talking about the ways in which they shaped that agenda and pushed the NIH to funds those types of studies. I can tell you that in my case I actually advocated against the financing of those types of projects. I'd be happy to talk with others about that at some other time, but just to set the record straight, I did not lobby for those in the context of the Environmental Genome Project because it seemed to me that that constituted a form of genetic exceptionalism.

But going back to the subject at hand here, I think when we look back on the Environmental Genome Project and that brief description that I just gave to you there, in many ways the project's agenda seems relatively non-controversial by today's standards, both ethically and politically. Especially when you compare it to other second-generation genome projects like the International Haplotype Map Project and other projects in which concepts of race and ethnicity were such major issues in terms of study sampling and study design. But I want to suggest that the Environmental Genome Project raised some special issues that I think are still relevant to the conversation today.

So let me talk about one of those issues or perhaps broadly a set of those issues, and these are issues that really emerged for me in the context of very specific discussions that I had with critics of the Environmental Genome Project while I was still involved. So various criticisms began to appear very soon after the project was announced, but most of them focused on specific methodological questions and questions about the project's potential utility. A very different set of criticisms came to my attention one afternoon when I got a call from a gentleman named Bill Freeman who at that time was the Director of Research for the Indian Health Service. Bill told me that a group of American Indian and Alaskan native advocates were organizing a formal demonstration in which they were planning to demonstrate and express concerns about the

Environmental Genome Project. Remember, I was ten years old, fresh out of graduate school, and the thought that there was this mobilized political activism about which I was supposed to somehow respond was really quite a thing in that day. These advocates were worried in particular that the Environmental Genome Project wasn't what it appeared to be and that in fact the project was an attempt to resurrect the Human Genome Diversity Project, a project that's well-known obviously to the group here at Stanford. These advocates claimed that researchers at the NIH were using the Environmental Genome Project as a front for collecting genetic materials from indigenous communities and that once those samples were in hand, they would be used by physical anthropologists and others to go and study patterns of human migration, relationships among indigenous communities and so forth. So two days after that phone call with Dr. Freeman, I was on a plane headed to Albuquerque where I met a number of those activists. Essentially my task as I understood it at the time was to talk to them about the differences between the Human Genome Diversity Project and the Environmental Genome Project. There was a lot of skepticism on their behalf about the differences that exist, and I think ultimately those did come through, not the least of which was that the Environmental Genome Project had no plans to sample from any indigenous communities. And through those conversations though, I came to appreciate what I know think is a much more fundamental ethical challenge in all of these gene-environment interaction studies.

So in Albuquerque, many of the people that I spoke with who were concerned about biomedical research that involved American Indians framed their concerns in relation to diabetes. Diabetes, they said, was not a problem for Indians until people in indigenous communities adopted relatively sedentary lifestyles and began eating more Western diets. So if a project like the Environmental Genome Project were to identify specific genetic factors that predisposed someone to diabetes, they said that that finding would be largely irrelevant to persons living in indigenous communities because the environmental factors that made diabetes an epidemic problem in those communities were already well-known. But more provocatively, what these advocates said was that a study of environmental contributions to diabetes in indigenous communities would only show that certain genetic factors predispose *some* individuals to diabetes, namely those persons who live in oppressive environments in which opportunities to pursue more healthy lifestyles are absent as a result of historical abuse and exploitation. So identifying specific genetic mutations associated with diabetes, from their perspective, might actually be detrimental to indigenous communities since these findings would suggest an alternative explanation of what many persons living in those in the communities regarded as the primary cause of diabetes, namely Westernization. Efforts to identify those genetic mutations might also be disrespectful in a peculiar way. Since studies of genetic contributions to conditions like diabetes would be viewed by these advocates as part of a more global pattern of neglect with respect to issues of concern to indigenous communities. For many in those communities, the Environmental Genome Project was just another example of the government investing in research with little to no relevance to what they considered to be their needs or interests in improving public health. *Genes* matter to research funding agencies, but the legacy of Westernization and the inadequate social resources available to persons living on Indian reservations don't matter.

So what I took away from those interactions with critics of the Environmental Genome Project was that studies of gene-environment interactions can fail to take seriously the social and

historical forces that have produced contemporary environmental hazards, contemporary diets, behavioral choices and so forth. And unlike genetics contributions to disease, environmental contributions to disease are not there, not there waiting to be identified by researchers. Genetic mutations are clearly inherited, but what we regard as environmental contributions to disease are constructed and reshaped over time.

So in a surprisingly way then, implicit in the study of gene-environment interactions may be a subtle presumption that the larger social and political forces that have given rise to a particular environmental hazard, or a current diet or something of that sort, some element within the environment, that those things are immutable or at least very difficult to change. In selecting particular aspects of the environment for study, say diet or exposure to an industrial hazard, researchers are defining one aspect of a complex environment as critical for health. Those specific elements of the environment are now what matter most in terms of efforts to improve public health and are put forward as those things that are deserving of attention for researchers. In this sense, there's an interesting parallel with the use of racial and ethnic categories in biomedical research more generally. Contemporary racial classifications are also the legacy for an oppressive history of discrimination yet they continue to be used widely in biomedical research. Critics of their use often claim that this approach is not only instrumentally harmful to socially disadvantaged racial and ethnic groups since those categories may exacerbate existing stigma or enable new forms of discrimination, but their use *reifies* biological distinctions among racial and ethnic groups as well. In the context of gene-environment interaction studies, the choice to focus on select environmental contributions to disease may give those socially constructed determinants of health an analogous importance that other elements of the lived environment lack.

So to return, to make this more concrete, to the example of diabetes, the environmental contributions to diabetes that matter in many studies of gene-environment interactions are dietary, not the larger by-products of Westernization, such an eroding tax base, inadequate rural health care or any number of larger social forces that one might choose to focus on instead. These larger forces are the backdrop against which studies of gene-environment interactions are framed and that often go unexamined in the selection of specific environmental factors to study. In searching for gene-environment interactions, we should ask whether we are implicitly condoning the continuance of these social and historical forces that have given rise to current environmental conditions or are we at least redirecting important resources from the problems that matter most with respect to advancing public health. That for me is what I now understand to be the implicit claim that the critics of the Environmental Genome Project were making when we met that afternoon in Albuquerque. And that's what I now regard as the most important of the ethical and policy challenges raised by studies of gene-environment interactions. Thank you.

***Sealing Complexity: Genetics, Social Structure and Policy Environments* - SS**

Not Transcribed

Discussion

AQ: Mostly for Professor Wise I guess, but for any of you, it seems to me that the flip side of personalized medicine is personalized insurance, which might be kind of surveillance and personalization of risk regime that we ought be worried about. If you could comment.

PW: Well you may want to comment more on this Hank than I, but I think it generates a whole series of policy questions. The reason I didn't mention it, to be real honest, is because with this crowd, it tends to be front and center with the policy questions that are generated by personalized medicine. However, while I think it's crucial, I think it is no larger a central challenge to social justice questions in the policy arena than many of the other kinds of considerations. Do you want to mention or comment on that?

HG: No. We'll go to another question, Ruth. Although I'll say that at its extreme, the idea of personalized insurance means no insurance at all.

RO: This is a question for Dr. Wise also. You made an interesting point saying that we will get new disease taxonomies from the discovery of new essentially webs of causation or gene-environment precursors. That's a very interesting concept because it seems that what you're getting at is that the very definition of a disease involves on classifying it on the basis of what causes it.

PW: No, sorry.

RO: But at the same time we know that there can be multiple different types of causes of the same set of clinical symptoms and that set of clinical symptoms might respond to treatments in a different way or it might not depending on what causes it. It's interesting to think about how we classify diseases vis-à-vis their causes, and I was wondering if you could elaborate a bit.

PW: Thank you. I was not arguing to classify diseases based on their causes, in fact quite the opposite. I was just suggesting that we would need new ways of classifying and re-aggregating our understandings of disease to fit our requirements of policy. For example, people have already begun to reclassify disease based on notions of critical periods of development, to begin to cluster disease states or behavioral states based on evidence that things are taking place very early in life like during gestational or before the kid reaches three years of age. And while I have lots of questions and skepticism, the whiffle ball analogy was a snide way of suggesting there may be more to it there. In the policy arena, it can cause great mischief. The idea has been to elevate early child development because of these critical periods; it's critical. However, if you say the ballgame is over by the time the kid reaches the age of three, it basically turns adolescent medicine into palliative care. And the kinds of impact it has on the policy conversation can be highly detrimental. So what my suggestion is that, and what I'm trying to do working with Atul in his group, is to begin the re-aggregation of these gene-environment interdependent clusters into categories that speak to the requirements of social justice, speak to the requirements of how policy interacts with science. That the representation, if not the science itself, implies the exercise of power, it implies ethics, and therefore how we re-aggregate given the breakdown of

our traditional aggregation of disease states based on organs and things like that, we have to be very intensive to the policy considerations.

HG: So if adolescent medicine is palliative care, is adult medicine all hospice?

PW: You called it, and in fact, pediatrics is…

HG: Thank you, thank you very much. You are a pediatrician.

PW: You see the thing that's happening to pediatrics is it's becoming increasingly the domain of pediatric management of adult onset disease. When someone says the biggest challenge to childhood health is obesity, they have transformed pediatrics into the management of precursor conditions to adult onset disease. Go to Packard Hospital. There are no kids in those hospital beds because they're obese. It's basically transforming of notion of what pediatric care is. We're not ready for it in pediatric care, we have no structures, no policies.

HG: Another question or two?

AQ: Question about the roles of community collaboration and defining sort of causal issues that seem to be addressed by policy. We've got nationally this movement towards more community involvement, particularly Richard's example, but earlier the Kaiser example, suggested we'll see very radical paradigm shifts in not only priorities, but also in what are considered causes that ought to be addressed. So I'm inviting Richard, you or the others, to just comment on where this might be heading.

RS: I think we're going to see a lot more calls for community-based participatory research in gene-environment interactions. That trend has already begun, and I think were going to see more of that. And I think that's something that, in terms of epistemological issues that are embedded in that, is gonna be kind of tricky. We think about community participation in classic genetic epistemologic *[sic]* research. We're asking for members of patient communities to get involved because we want input in terms of how to operationalize the study. How do we go about recruiting; how do we go about appropriate informed consent documents and so forth that are sensitive to community interests and needs. I think in the context of gene-environment interaction studies there may be a number of communities that want a richer role in the design of those studies. That it's not about operationalizing a study; it's about designing a study. It's about selecting particular environmental determinants to investigate and so forth. So this movement to CVPR research is going to pose a number of epistemological challenges for investigators as it moves ahead.

AQ: Actually, quite a similar question and I'll address this to Dr. Shostak. Kenneth Olden said that one of his achievements was redefining the environment, and I noticed that WEACT was one of your sites. And I'm wondering if it was the interaction with WEACT, I know that the NIEHS has formal relationships with WEACT, which is a community-based justice organization. How did that interaction work and is there a model there that we can use to start defining questions, basic questions?

SS: That's a great question, and I don't know as much towards the answer as I'd like. So WEACT as West Harlem Environmental Action; it's an environmental justice organization in Northern Manhattan. They have received support from the National Institute of Environmental Health Sciences and also the EPA to create forums in which questions about genetics, the environment and communities of color can be addressed. That specific topic was at the center of a two-day meting in 2002, and the collaboration has moved forward especially with researchers at the School of Public Health at Columbia University. So I think one question we could ask, not just of that collaboration, but more generally is, now I'm doing one of my favorite things which is thinking about research topics for someone else, is *[sic]* to think about what the different models are of collaboration between environmental health and justice groups, university-based environmental health science centers and you know kind of with, sometimes possibly without, the support of the federal agencies whether NIEHS or EPA. And if we can think then about the models then from different social actors perspectives that have been more or less effective in advancing their collaborative agendas, that the WEACT, NIEHS, Columbia group has done a fair amount of publishing, collaborative publishing, so that does seem like one place to start.

HG: Ok, well join me in thanking this panel.

End Panel 4 and Discussion