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PROCEEDINGSI. Orientation and Welcome

Kathleen Michels:

Okay. Good morning, everybody. I know people are still coming in, but we need to -- we're -- this meeting -- whole symposium is being videocast, and we have a very packed agenda. So we're going to start in one minute, so if everybody could get settled in. If you don't have your badge, then you can get your badge at the break.

All right. Well, good morning, everybody. I'm so happy to see all of you and really just want to welcome you to the celebration of a decade of wonderful research collaboration around the world, under the Brain Disorders in the Developing World Program with a focus on research across the lifespan. I am Kathleen Michels. Many of you know me, but for those of you who don't, I've had the privilege and the pleasure to be the Program Officer for this program and be involved in it, essentially, before it was born. So it's wonderful to see it now a decade later.

I'm sorry that we can't do full justice to all of the wonderful research under the program. We have an embarrassment of riches under this program, and so there's a lot of gems that won't be exhibited today. But certainly we have -- we'll have a lot of time during the discussions, presentations, at the breaks, and the reception today -- which will be at 5:30 -- to really dig into some of the presentations -- some of the windows that are opened through the presentations today.

I want to thank especially all of the NIH institutes and centers that have been partners with us throughout the years in this program. Without them, the program really couldn't have happened. And I also want to thank my -- the wonderful staff that's worked on this program, in particular Francine Sellers and Farah Bader, who have been program specialists, and analysts on the program throughout the years, and whom you have heard from, both of them. And so, in addition to the rest of the team, who I'll mention later for time, they've -- really want to give them a round of applause, actually, right now.

[applause]

And I also want to thank the symposium sponsors for making this happen. This -- in particular the National Institute on Aging

for providing the funding for the videocasting. Everything good about this symposium and the brainstorming day to follow are thanks to all of our incredible staff, and any problems I take credit for.

Some quick housekeeping. There'll always be someone at the registration desk: please refer to them for any problems, questions, and for information including taxis and food. If they don't know, they will find out. We have a couple of speakers that we'll mention later who Congress has stolen away from us, but we have some wonderful people to fill in.

So, without further ado, I would like to introduce the Director of the Fogarty International Center, Dr. Roger Glass, who is also Associate Director for the International Research arm of the NIH.

[applause]

II. Welcome and Overview

Roger Glass:

Thank you, Kathy. I'm really delighted to be here. This is one of my favorite programs in our portfolio at Fogarty, and I stand here with two hats. One is that I have a vested interest I have to alert you to. I am the Director of the Fogarty and this a Begins at Fogarty program, but I also have a second hat, which is the Associate Director of NIH, where I'm trying to encourage the different institutes at NIH, with the help of Dr. Collins, to get involved in the Global Health agenda. And so this is a program that really does that in spades, and there are eight other institutes and centers that have been involved in this program, so it's exactly where we want to be.

Now when I -- Kathy asked me to speak -- you know, I'm a bystander to this program, because it began before I became Director. Gerry Keusch was my predecessor, and I was thinking about what to say to you, I began thinking back 10 years ago, and I was saying "What was Gerry Keusch smoking at that time?" What encouraged him to think about global mental health as a problem? Was there big money? Were there big problems? Was there a global uprising of interests? What was it that got him to do this? Because it was really, as we look back, way ahead of its time. And, not only Gerry, but what were the institutes thinking? Steve Hyman, how crazy were you 10 years ago to think that this was something important to do?

So, I've been contemplating that, and as I've looked over the quality of the research and what's happened, I've come to see that there was tremendous wisdom in the skiddiness you must have had to set out on this path a long time ago. Not only you, Steve, but the directors and the program officers of the eight other institutes and centers here.

Well, you know, here we are, in Washington, D.C., and I'm called upon repeatedly to go downtown by a congressman who says, "Why should we be putting money in global health? We've got enough problems at home. We can't support our own researchers; what's in it for us? What's the goal here? What are we going to gain?" And I think, if anything else, the programs that you're going to hear and the research you're going to hear over the next day or two are really going to demonstrate the answer to this question.

You know, the summary of the data is easy to present. Over the past 10 years, there have been 119 R-21s, 37 RO-1s. Lots of publications, lots of long-term trainees, tremendous partnerships between U.S. and foreign institutions. So there's been a tremendous amount of activities in 36 countries, nine ICs involved together. These are the data. But, you know, Einstein had a famous quote that says, "All that we can count does not necessarily count, and what counts often cannot be counted." And I think that the stories that we're going to hear will be that which is difficult to count, but is really the meat and grist of this amazing program.

Well, one of the rationales for NIH to become involved in global health and global health research is because we're looking for opportunities that we can't find at home. And this is written in our mandate here, as you can see, we're looking for the use of unusual talents -- and that's many of you in the audience from overseas -- unusual resources, populations, environmental conditions, diets, genetic pools, that we can't find anywhere else or we can find better overseas. So that's really our rationale, and as long as this is in the mission of our institutes, we can go there, so it gives us a hunting license to partner globally. And also, there's the issue of peer review, which is the mainstay of what we do and which also means that all of you who are here have, by being here, shown that you're incredibly competitive in the scientific community.

So where are these programs taking us, and what is this lifespan bit that we're talking about? I see this in a number of our programs. Well, lifespan -- and it's interesting, from this

map, as you can see, lifespan for neurologic complications, neurologic diseases, goes from pregnancy, things like fetal alcohol syndrome, to early childhood with diet and genetics, to, in Epilepsy, Hydrocephalus, Malaria, to adulthood and aging, Alzheimer's and some of the consequences, and stroke. So it's really the lifespan, and why do we go overseas and aren't these diseases that we can find at home?

Well, we have Fetal Alcohol Syndrome in the United States; it's almost gone away. But to study and understand it and understand how to prevent it, the opportunities really exist overseas and our ability to intervene and understand exist overseas. So, these are not only problems overseas, but they're problems that influence us at home, and I want to give you a few nice demonstrations.

Well, the other thing we do at Fogarty and that this program highlighted, is a feature that I call, if you will, early childhood education, early career education. Which is, that if you get people young in their career, and you put them in an interesting environment, you may be able to permanently change their brains and their careers and their global outlook. So I wanted to start with this slide of a young woman who's in the audience, Gretchen Birbeck, who decided to go off to Africa on her own as a young neurologist, at the disgruntlement of her Chief of Neurology, who said, "What the heck are you going to learn there? You're throwing out a wonderful career." The same thing that my wife's boss said when we went to Bangladesh when she was just finishing her fellowship, and now she's Chair of Pediatrics. So, some of these people who have thrown out their careers by going overseas have actually done quite well. And it's a secret, I guess, we shouldn't reveal.

And also, why would a congressman want us to study evil eye in Africa? I mean, this is really a hocus pocus, zombie medicine. Well, I think this is incredibly interesting, and I think Gretchen's career -- and she'll speak about this -- is demonstrative that early childhood education or early career engagement in global health research can make a permanent difference in a person's life and their career and their ability to affect change and bring some of that change back home. So she's been involved and funded now fully with her partners through NINDS on stigma around epilepsy and low-cost treatments of epilepsy. When she went to her community, epilepsy was not a problem because in the total community, there were only about 30 patients in a huge population with seizure disorders. When she went out and did the study, there were 2,000. So they had

missed only by 99 percent. So, just by bringing epidemiologic tools and since to the field, you can actually identify problems that are clearly there, but are not seen even by those closest to them. So this is an example of what this program has been able to do.

How about Fetal Alcohol Syndrome? We'll hear presentations, supported by NIAAA -- Ken Warren is here -- in Russia. And why should this be so interesting to us in the United States, and I'm thinking about my congressman downtown, and I can actually say that while we've been able -- we had this problem, we still have this problem in the United States in low numbers, we also have many orphans who come to this country from Russia, from orphanages where mothers have given up their babies because they've been single, they've been binge drinkers, and where their children have some evidence of Fetal Alcohol Syndrome. So it's something that affects us right here at home. It's an opportunity to study, to intervene, and to understand, and I think this program is demonstrative of that part of the life span.

Dick Guerrant, an old friend from the diarrhea field who, through this grant, made some unusual observations about the APOE-4 allele in Brazilian children with diarrhea. Now we all -- I've known Dick for his work on diarrhea, but when he got into thinking about APOE and Alzheimer's, I said, "What is Dick smoking? What's going on with him that he's found this unusual association, whereby this particular allele protects these malnourished children in Brazil against diarrhea and malnutrition, but also predisposes them to Alzheimer's later in life?" So, it's an unusual attempt to understand a very important risk factor -- genetic risk factor for Alzheimer's in our own population.

And then I go on to Ben Warf, who I just met this morning but I've known about for ages. What kind of a kooky neurosurgeon -- pediatric neurosurgeon goes to Africa for six years after training? What can he learn there? Why is this so important? And because he abandoned his career at Harvard to go to Uganda, he got the MacArthur Award for unusual studies on the ability to treat hydrocephalus surgically and without retreatment. So in the recognition by the MacArthur Foundation, they said, "A man that through his research practice teaching and organizing activities, Warf is demonstrating that the standards of healthcare can be improved alongside access to that care, in both developing and the developed world." Ideas that have come from the developing world have come right back to help us at

home, and change the way we think about global health, and a treatable disease.

How about in the Rakai, a field site in Uganda that we've supported for AIDS research through Fogarty, NIAID, and many of the institutes for a long time, and has been instrumental in promoting issues like circumcision for the prevention of HIV. Well, here you see Ned Sacktor and Noeline Nakasujja working on neurologic AIDS, a major problem in patients with AIDS and a major problem in differentiating between different subtypes and their presentations of neurologic disease. Clearly important for AIDS patients in Africa, perhaps for AIDS patients in the United States, but understanding that link between HIV and neurologic disease.

Joe Zunt, in the audience as well, and Silvia Montano working in Peru for a long time, training another generation, early career development, early childhood education through our Fogarty Fellows program on neurologic disease in that setting. Very important work and a beachhead for research in the global health arena.

You're going to hear now from Desire Tshala-Katumbay working on cassava toxicity. Is this a problem in the world? Well, there are only 600 million who eat cassava as their staple starch, and because of the problems -- he has been a unique investigator with his team and thinking about the neurotoxicity of this plant and its detoxification and issues around it. An amazing study, incredibly important as we think about the developing world, and issues of whether some of that problems of development, couldn't be directly related to nutrition. So, we welcome Desire with his extraordinary work. Thank you.

And then when I talk to that congressman again, and as I've heard in the congressional reports, a third of Americans will come down with this disease, Alzheimer's, in our later life. And it's going to bankrupt our healthcare system. We need research now, so that we are not bankrupting our system in the future, and this is something that affects all of us who plan on aging. Do any of you plan on aging? I asked that to the congressman. I said, "Are there any people in your constituency who are aging?" And he had to agree that there were, and I said, "Where's the most interesting research going to come from on aging? How will we figure out how to deal with Alzheimer's?" And he really didn't know, and I said, "How about Colombia?" And this was an article on the front page of the New York Times, which means it has to be important. And it was about

Alzheimer's in Colombia, a family tree that dates back to 1745 of patients with an Alzheimer's gene, that's been followed through the generations and is now the topic of research by one of these grants through NIA in this Brain Initiative.

Ken Kosik and Francisco Lopera are working on this unusual presentation, this genetic disease that causes Alzheimer's. Gloria Patricia Cardona-Gomez will be here speaking with us, but here we have a disease with high prevalence, early penetrance, and rapid progression. So if we're interested in biomarkers of disease or treatment, this is where we have to go to find it.

The unique model to stimulate research. So, in conclusion, this Brain Initiative has given us a unique model to stimulate research in global health. We've developed extraordinary partnerships over the past decade, which will be enduring as we go forward. We've developed a research capacity at home, as well as abroad, in these issues of global, neurocognitive disorders, neurologic disorders, and we've identified novel opportunities, populations, exposures, and outstanding individuals -- you all. And so this is a program that's been way ahead of its time.

Where do we go from here? What can we do in the next decade of this program? We have built a strong training base, we have researchers who are competitive, we have eight -- nine institutes and centers at NIH that are engaged, but how about globally? There's the Global Alliance for Chronic Diseases, which is a network of about a dozen medical research councils around the world, that provide funding for about 80 percent of the research funding in the world. They met in the U.K. in December, at the time of a dementia summit. Maybe this is the time for a brain summit to push this agenda globally.

There's the U.S.-European Union Stroke Consortium, the U.S.-U.K. Traumatic Brain Injury partnerships. So there's a lot that we could do this activity as we go forward, and funding opportunities because these are diseases which affect us all. In fact, in the consortium of NIH, we have about a dozen institutes -- of our 27 institutes at NIH, about a dozen of them deal with neuroscience. So, in fact, neuroscience as a whole is the largest single focus -- the brain is the largest single focus group of our research, even though we are divided into 12 separate entities.

We also have -- when we look at the impact of this program in our world report, looking at documentation of research by NIH in

Africa, about 15 of the 35 grants that NIH supports and that the world supports in African neuroscience are from this initiative. So, we are representing about 42 percent of all the neurologic research in Africa in granting through this program.

This program has been so well conducted and so well appreciated at NIH that it received a Director's Award. And you can see on the stage here, Dr. Collins giving Kathleen Michels and that entire team of project officers this award. Are those project officers all in the audience? Because I think if you are, you should stand up. You are the ones who have carried this program forward forth. You want to stand up, all of you project officers?

[applause]

I only see one or two, but -- okay. They're the ones who have made it happen, and supported by their directors. You know, Dr. Collins has made global health one of his five priority pillars of his administration; he's been incredibly supportive. Why does a geneticist, a basic scientist interested in global health, you might ask, just as I've asked before, what was he smoking? Well, he was, as a young physician, sent or chose to go to Nigeria to work clinically as an internist and found the experience so moving and actually found patients with diabetes that didn't have a normal presentation. And this lead him to look for the genes, and identify the first genes of diabetes. So he sees this as a tremendous learning opportunity, as well as a humanitarian opportunity. He has been incredibly supportive of the global health agenda.

Of course the world is behind the non-communicable disease agenda, we met at the U.N., it seemed impossible a decade ago, and yet, in 2011, it happened. And so of the NCD agenda that's moving forward, I would say that the agenda for neurologic disease is really by far the most advanced. So you people are ahead of your curve. This is the time to seize the hour, to move ahead, and to think about some of these common risk factors for your diseases. Think about nicotine addiction and tobacco; think about salt restriction and stroke; think about alcohol as the number one potent drug, toxic drug in the world; think about drugs and nutrition and the diets that we are going to hear about.

I have a paid political advertisement here for our Fogarty Fellows and Scholars Program, but it is supported by 16 different institutes and centers. This is our way to capture

young investigators, pre-docs, and post-docs, like Gretchen Birbeck, but like local investigators in post-doc levels to come and have a year of funded research through this Fogarty program. It's a way that we've captured scholars and fellows. You can see a neurologist right here in the middle, Joe Zunt, who's been a tremendous asset to training neurologists through this program. So I encourage you all to think about this as a way to get the next generation trained.

And we also have the MEPI Program with Fogarty, which has provided platforms throughout Africa for building of medical schools. Five of the linked awards are in neuroscience, and we think this is a nice bedrock for further research.

So in closing, congratulations. And the congratulations are not from me; the congratulations are for all of you. For the institutes and the institute directors who have put their emphasis, time, commitment, and finances behind the program and the program officers. To you as investigators because over a decade, you have proven through your work that this is a -- you've made valuable contributions. You're all making a difference, and I'm looking forward to participating and hearing the results of this decade of research if which you've all been involved. Thank you so much for all you've done. Thank you.

[applause]

Kathleen Michels:

Thank you very much, Dr. Glass, for that whirlwind tour of the program.

III. Keynote Speakers on the Value of Research and Capacity Building in the Developing World

Taking the Global Burden of Brain Disorders Seriously: Why so slow?

Kathleen Michels:

I'd like to introduce now Dr. Steven Hyman. Dr. Hyman is Director of the Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard and is also a Harvard University Distinguished Service Professor of Stem Cell and Regenerative Biology. From 2001 to 2011, Dr. Hyman served as Provost of Harvard University, and I won't go through all of the [laughs] -- I'm going to give some highlights but a couple of other things. Of course as you all know, from 1996 to 2001, Dr. Hyman served as Director of the U.S. National Institute of

Mental Health. And Dr. Hyman is also Editor of the Annual Review of Neuroscience, President Elect of the Society of Neuroscience -- congratulations -- and founding President of the International Neuroethics Society, and member of the Institute of Medicine of the U.S. National Academies.

So, thank you very much, and we welcome Dr. Hyman.

[applause]

Steven Hyman:

Well, it's a real pleasure to be here 10 years on, and I actually don't remember smoking anything. I remember actually - it might have helped. I remember being very frustrated about the lack of attention to brain disorders. And indeed, that's what I want to reflect on.

I was asked to speak on the value of research and capacity building, and of course, who could be against it? But the question really is, for me, how is going to get implemented? How is it going to make a difference? So, let me just -- one slide on reflecting on ten years of research, and I've taken, as an example, not surprisingly, something that I know well, and work on. But 10 years ago, many monogenic neurologic disorders had their genes identified and while that hasn't yet issued into therapies from many of these disorders, there is a deepening understanding. But no one could have imagined 10 years ago that we would now have for polygenic common disorders, like schizophrenia, bipolar disorder, autism, and also many diverse monogenic forms of intellectual disability, genetic programs that are going to help us, we hope, make progress in understand and in therapeutics. So, for example, in -- little bit sensitive here. Are we -- Yeah. All right. But suffice to say, that the technologies that have come out of the Genome Project and following give us enormous hope for global basic research in mental, substance abuse, neurologic disorders, and we look forward to this progress.

At the same time, however, very important priorities have been identified in the global health context with a focus on the developing world. And for at least mental disorders, Pam Collins, who's in the audience, led an important exercise to identify important goals -- the term "grand challenges" is in vogue, but these certainly are important goals that are very much related to the general research in MNS disorders, but also to the developing world context. So, the identification of risk

and protective factors, including the impact of war, poverty, migration, and disaster.

But of course, it's not that the United States and the developed world aren't involved in just in these kinds of issues, whether it's our current wars in the Middle East with returning soldiers with PTSD and traumatic brain injury or Hurricane Katrina. So again, these issues generalize.

We need to improve treatments and expand access and integrate treatment into primary care. Again, a major goal in the developing world, but also of critical importance here at home in the United States. I think I'm echoing some of Roger's sentiments. We need to improve children's access to evidence-based care, and again, in the developing world, kids with developmental neuropsychiatric disorders often are invisible. Kids with ADHD, learning disabilities really can't live up to their potential.

But the same is true in a lot of the developed world, and we need to strengthen training on mental, neurologic, and substance use disorders across all healthcare professionals, and again, this is really a global issue. But instead of focusing on the individual bits of research, which you'll hear about later today, which you'll see in the posters, what I want to focus on is the gap between what we know and what we do. And I think that gap is unconscionable.

Again, you'll see this, probably several times, but what it shows is that -- this is the recent Lancet series showing the latest global burden of disease statistics, and in red are the mental disorders and substance abuse disorders, and here are the neurologic disorders, with mental disorders having their largest burden early in life, especially in the 15 to 44 age group. They take the greatest toll on disability, they're -- they are accounted for about 23 percent of all dallies worldwide; the neurologic disorders always with us, but obviously increase, as Roger pointed out, with aging.

So these have been very well documented many times over, beginning in 1996 with the first GBD study that Chris Murray did as critical contributors to burden of disease. More recently, the World Economic forum and the Harvard School of Public Health looked at the lost output attributable to non-communicable diseases, and -- I apologize to the neurologists, they've just broke out mental disorders, which presumably, again, includes

substance use disorders, but 35 percent of lost economic output was attributed to this class of illnesses.

And I don't have to tell you that as the world population ages, so -- this is simply the staggering growth of the world population projected out to 2050 by the U.N. This is the percentage of the population over 60. We're going to see much more in the way of neurologic disorders, especially neurodegenerative disorders, but at the same time, because of rapid urbanization, conflict, and post-conflict situations, there is an increase in prevalence of a number of mental disorders that we see in younger people.

Why is the burden so high? You know, is this credible? Well, one issue is that there's very high aggregate prevalence. I won't take you through the numbers but, major depressive disorder is extremely prevalent, both in high-income countries, and low and middle-income countries. The age of onset, and the same could be said of alcohol and substance abuse disorders, the age of onset of autism even earlier; the age of onset of schizophrenia, mid-teen years, and so forth. So, early life onset of disorders. Typical course is either relapsing, remitting, or chronic. And, of course, the brain is the organ of cognition of emotion regulation, and executive function -- control over behavior. So if your brain isn't working well for you, you're not going to do very well in school, you're not going to be able to work. So, again, we could go on for a long time, but the point is that the burden -- statistics that come up in the GBD studies, where -- again, disability's the hardest thing to measure credibly -- is corroborated by many additional facts.

The societal costs, then, are enormous, in terms of years of life lost to disability, the global burden both for aging population and neurodevelopmental populations, both on the people who are affected themselves, but also the caregiver burden is enormous and costly. Neurodevelopmental disorders continue to degrade human capital formation. Mental disorders are a significant strain on the criminal justice system. This Sunday, if you picked up the New York Times, Nick Kristof, who normally writes on human rights issues, wrote about the U.S. prison system as being the largest mental -- set of mental hospitals in the United States. And the people complaining were not mental health advocates, they were the Sheriffs Association, who basically said they're overwhelmed and don't know how to handle people humanely or effectively. And there are also of

course significant negative interactions with other chronic diseases: Type 2 Diabetes, cardiovascular disease, and so forth.

So here's the central conundrum, and this is the point of why I was rehearsing what you will hear again from many, many speakers, which is this data doesn't seem to be making much of an impression on policy makers. I was just, less than a month ago, at a really wonderful meeting held in Addis Ababa about the formularies available in sub-Saharan Africa -- the effective formulas, not the official formulas, but the effective formularies for many countries for epilepsy, schizophrenia, and depression. And, for the most part, the formularies -- that is, the drugs actually stocked and available, not drugs that were written down somewhere -- were 1950s drugs. Chlorpromazine, the very first anti-psychotic, discovered in 1951; Amitriptyline, a drug so toxic, in terms of both side effects and -- a week's supply you could kill yourself with, that as a -- when I was practicing psychiatry, I found it almost impossible to get any human being onto a therapeutic dose, because they couldn't stand the side effects. And of course, Phenobarbital is not a great way to be alert in school for the many children with epilepsy, and there are many studies showing that chronic Phenobarbital use may have a deleterious effect on IQ and so forth.

So, we had this great meeting, but when I left -- I have to say, and this is my own personal impression -- everybody wanted to make a difference. Everybody understood that supply chains, exemplary supply chains existed for treating infectious disease. Everybody understood the importance. I didn't get the sense that anyone was fully committed to changing these formularies. And so the question is, you know, what is it about these disorders?

The -- we heard about the high-level meeting of the General Assembly in 2011 on NCDs. Actually, I found it incredibly disappointing, even though risk factors for brain disorders -- like tobacco control and stroke prevention through salt restriction -- are a figure in the outcome, but in fact the brain disorders were not represented. And, in fact, the GBD data, the Global Burden of Disease data, is WHO data; it is U.N. data. And yet, the list of officially represented diseases excluded brain disorders despite a certain amount of belated lobbying on the part of people interested in mental substance use and neurologic disorders.

And I think the question again is, how is this possible that aside from -- I would never imagine that low politics and

maneuvering for position and funding had anything to do with it -- how is it possible for the U.N. to ignore its own data about the leading causes of dailies? And then another problem, of course, that we now face is that industry -- has 2010, has been progressively exiting central nervous system disorder. So, still a very large effort in Alzheimer's clinical trials, but a number of companies have said, "Look, if the latest crop of trial aimed at A-beta as a target fail, we just can't afford to go on in this area."

So the idea is brain disorders are seen as, quote, "too difficult." There's a limited number of mechanism, although again, this is changing as genetics and new models, stem cell model become available, and for many diseases, there are still no biomarkers, which, again, is a major problem. We can't appeal to businesses to do something for moral and ethical reasons, to say that there is all of this severe, unmet medical need, all of this disease burden. And yet, there is remarkably little uproar, or even recognition, that industry is walking away from central nervous system disorders.

Okay. Well, you know there's some reason, some thoughts about why these disorders have been prioritized, and of course it's easiest to deprioritize mental disorders, substance abuse disorders, and those neurologic disorders without clear stigmata. So nobody doubts Parkinson's disease, but in many parts of the world, Epilepsy, even though there may be grand mal seizures, remain very much in the shadow. You know, there's a sense that for many of these, there are no objective medical diagnoses, but in fact, for conditions like Schizophrenia, major depression -- in fact, clinical diagnoses are really quite good enough to prescribe the existing drugs. And one thing which is really important is -- which we'll come to at the bottom, but I might as well do out of order, -- a lot of people say well, the existing treatments are not good enough, or they're too expensive. But in fact, there are cost-effective, largely [laughs] here thanks to the lack of progress, sadly, off-patent antidepressants that are modern and, you know, not efficacious enough perhaps, but certainly efficacious well beyond placebo and nontoxic, second generation antipsychotic drugs and multiple anticonvulsants that could be marshalled -- and this was the point of this conference in Ethiopia. There is a sense on many people's part that maybe these disorders are not severe enough, that, you know -- yes, depression is common but maybe a lot of these people really just need to tough it out. You know, this is just transient sadness.

A lot of research shows that that's not true. That, you know, there's a lot of corroboration of the disability numbers, and that the number of people who seek clinical care tend to be at least moderate and often severe. In many parts of the world, conditions like ADHD are said to be just, sort of, teachers who don't know how to teach and, you know, annoying kids. You know, in fact, ADHD is one of the most heritable of any common illness, the heritabilities are in the range of 0.8; it's got real brain pathology. And by the way, kid in the sort of left, bottom 2 to 3 percent of the bell curve, really do very terribly in school and in life, they're overrepresented among incarcerated youth. So while society is arguing about whether, you know, boys in prep schools ought to be getting Ritalin to help them do their homework, you know, there is -- there are really severe cases out there, often also co-morbid with ASDs, autism spectrum disorders, and so forth. And substance use disorders are seen -- whatever people say, often very unsympathetically. Even among some mental health advocates, they're passing the stigma buck as if, well but, you know, depression is involuntary, and so -- you know. I won't go into this, but it remains, I believe, a very serious problem.

Okay. So let's assume that policy makers are educated, and that they can at least get beyond simple issues of stigma. That is, even if a person with schizophrenia might frighten them on the street, they can isolate themselves from this. And even if they somehow moralize about substance use disorders, that they can understand that these are major societal problems. This is sort of -- this part of my talk I just pondered. This is the last few slides, but in some sense, I think this is -- we need to think about -- we need to really ask ourselves as we keep producing this data, as we produce the kind of research that Roger has reviewed, that really shows the ability to do something, but we still have this enormous treatment gap across the MNS disorders. What is it? Why don't policy makers act as if they believe that these are real and serious? And I think that it's that these policy makers are subject to -- you know, I don't know how many of you have read Danny Conoman about, you know, human cognitive distortions -- but I think there's something about, especially mental illness and substance use disorders, but also many neurologic disorders that interfere with their ability to see these as priorities. And I really do think we need to understand why they are, these diseases are not seen as the equivalent of other diseases.

So, very quickly, without getting too philosophical, you know, we're all sort of closet Cartesians. You know, like Descartes,

we introspect. And when we introspect, we think we understand what's going on in our minds, we think we understand our motives and our decision making, but we don't. Cognitive mechanisms, emotional mechanisms are opaque to introspection, and you can't actually -- although, behavior is involved in many, many chronic diseases -- you can't actually will depression away, or schizophrenia away. Yes, you have to be engaged to treat these disorders and substance use disorders, but it's not so simple. The MNS disorders, including suicide, are falsely thought to be under greater voluntary control than they are, and somehow, even though we know that many chronic medical disorders involve behavior, which also by the way -- people don't you know sit around and say, I know what I'm going to do with my life. I'm going to be morbidly obese, I'm going to be an alcoholic. I mean it's really -- I don't want to get into the details -- it's really not that simple, but often I think policy makers assume that these disorders can take care of themselves if people really tried. So we need to do another kind of research project, or else we're never going to close this gap.

We keep producing this wonderful data, but the UN --educated people managed to ignore their own data, right? So we have to hypothesize that somehow, there's a reason for this information not sinking in. And I would suggest we need to understand -- this may not be a Fogarty project -- and address those aspects of decision making that are palpably irrational and damaging to the health of those affected by MNS disorders and their caregivers.

Thank you very much.

[applause]

Kathleen Michels:

Thank you very much, Dr. Hyman.

Brain Drain to Brain Gain: Research Capacity Building and the Diaspora

Kathleen Michels:

I'd like to now introduce Dr. Desire Tshala-Katumbay, who's been involved since very early on. Dr. Katumbay will talk a little bit more about himself, so I won't say too much, because he'll be talking about brain drain to brain game.

[applause]

Desire Tshala-Katumbay:

Thank you very much for that invitation, and it's a really great pleasure for me to be here as a keynote speaker this morning.

I have been a Fogarty grantee for about seven years, and I would say fairly that 10 years ago I made a decision that was very controversial. I decided to leave the Congo -- I am originally from Africa, I am from Central Africa, from the Congo -- and move to the United States. And I'm going straight to the subject matter by saying that at the time I made the decision, I was thinking to come to the United States to get the training and get the money to go and do research, train the young people in the Congo, and make an impact in the lives of my own people that I left in the Congo. And I should say officially here that with the support from NIH, from Fogarty, and from NIHS, I do not regret my decision.

I am among those who say, "Let the young people -- let the brain circulate." I am those against program that fights brain drain because I do believe that with all the changes that we see around the world now, it's important that we let people circulate, get knowledge, and be able to make impact in the life of the home people. And I'm going to discuss with you what I have been doing for the last 10 years. In two different sections, I will give you background on my research work, but I will also talk a little bit about the capacity building that is associated with the research work.

And as you can see there, I focus on food and toxins in the developing world. Our main study sight is in the Congo, which is the previous Zaire, and actually the contest changed the name several times, from the Belgian Congo to Zaire to the Republic of Congo to Democratic Republic of Congo and now the Kinshasa or the Congo-Kinshasa.

So, I am a typical member of the diaspora community. And why one would think that it's important to get the diaspora engaged in the research for several reasons. But I have two favorite quotes -- I'm sorry -- that you can see on that slide there. Yes. So, yes.

So 2009, there is a nice paper in "Academic Medicine" that discusses why should a university harness in the diaspora community. And I strongly believe -- this is a paper by Nalini Anand and Dr. Richard Glass [unintelligible] was a cowriter on that paper. That the diaspora -- the members of the diaspora have a unique profile in the sense that they've been trained

across country and across culture. They've got experience from both sides, but at the same time, they can act as catalysts to make bridge or to build bridges between countries and communities. And this is an important thing to do if you want to make lasting contribution to the global health subject, and I will talk about a little bit later.

The second thing is that it's important, as I did myself, to be able to get trained to address the challenges. There are certain type of challenges that you cannot address if you stay isolated by yourself in a certain place around the world, it's just impossible. But why personally, I've decided to come to this country, get the training and get the funds, and to do what I am doing now.

And you can see, born in Zaire -- that was Zaire, that was me, many years ago.

[laughter]

Still very young, but the picture's still there, so still alive. Got my training as a neurologist in Zaire 1996. And then I moved to Sweden, get more civilized there. From 1996 to 2001, I got my training in clinical neurophysiology, I do my doctoral thesis there, and then from Sweden, I moved to the U.S., worked at the Oregon Health & Science University, and I moved to the U.S. with the help of IBRO, which is an international organization that deals with brain research. So I got a post-doctoral fellowship from IBRO to come to the U.S. to study the issues of food toxins. And I did my post-doctoral training at Oregon Health and Science University, and after my post-doctoral training, I learned how to write grants, how to submit an edge grant. I got a [unintelligible] from NIEHS. I trained for five years in molecular biology and neuropathology, because I was thinking, mechanism of the disease.

After those five years, I applied to NIH Fogarty for an R-21 grant to go back to the Congo and demonstrate to the Fogarty that being from the Congo, I could go back and show the feasibility of more intensive studies because the subject I'm going to discuss with you now 10 years ago, one of my previous mentors, Professor Osrosslin [spelled phonetically] and my doctoral thesis supervisor, Professor Torkild Tylleskär in Bergen, they were on this stage talking about the issues of cassava toxicity with a disease the is called Konzo, and the mechanism was still unknown. So I decided to start addressing that mechanism.

So I got that grant from NIH, NIEHS and Fogarty, and then after two years, we have been able to demonstrate that we could go onto a different level of research activity and capacity building. We put in a grant application and we got an RO-1. And today, I'm very pleased, for the first time, to show that many years ago, it was almost impossible to get young scientists from the Congo, train, come to the U.S., visit the lab, go back to the Congo. Because everybody was about seeing people leaving the country forever. But today they come and they go back.

I am very pleased to introduce to you, my colleagues. I have four in front of you there from the Congo coming to visit.

[applause]

So they are visiting, and I am going to tell you a little bit more about what they are doing. So -- and this was the journey, actually, inside that diaspora business. The subject that we focus on is called Konzo, and the disease, as you can see here, actually has been known for, as I said, almost for a century. This is the profile of the disease, and you can see how those subjects can walk, they have problem walking, they get paralyzed. The disease mostly affects women, but also children.

It has been known; it has been around for many years. And so far the mechanisms are still unknown, but we are getting there. And the disease has been described in many countries of sub-Saharan Africa, and you can see the red one in the Republic -- the Democratic Republic of Congo, in Mozambique, in Angola, Tanzania, Uganda, Central African Republic, and Cameroon. And you can see, also, on that slide that's not only, that the subject present with the paralysis. They can also present with high movement disorders, but also some type of optic neuropathy.

And we also, for the first time, demonstrated that this subject here do present with cognitive impairment, which is an important question to be considered now since we know that this is a diet for more than 600 people around the world. So we have been studying this disease, and we know so far that there are several things they are involved in. The plants themselves -- this is cassava -- which need to be detoxified when it's touching water, and when not touching water, it produce. So the linamarin, the toxic component in the cassava, get hydrolyzed into hydrogen cyanide -- actually produce hydrogen cyanide after processing the cassava water -- but if you don't have enough processing, you ingest -- oral ingest that type of food that is not well

processed, you get linamarin into your body, and the gut flora can either detoxify your linamarin or, if you can't detoxify it completely, you get intoxicated, you produce cyanide, and cyanide can lead to the production of [unintelligible] or to the production of cyanate, which is also a motor system toxin.

So, what else have we learned? We have learned, for instance, that there are some kind of key risk factor in this. So, apart from the genetic matter -- that I'm going to mention something about it, but not in very detail, because they are still work in progress -- we have found that, for instance, there are some key factor that actually plays a role in modulating the risk of the disease. And one of these is nutrition.

If you have poor nutrition, poor protein intake, you would be in trouble because you may have a very, very low capability to detoxify cyanide. For instance, we have seen that in those populations, because we conduct studies across species, we do studies in rodent, we do study in primate, in collaboration an institution in the U.S. here, but we also do studies in human. We have shown, for instance, that in rodent -- in the brain, rodent -- you need 10 millisecond to detoxify one morel of cyanide. In the plasma, you need about 1,000 millisecond. And if you look at the cyanide detoxification capability of the subject affected by the Konzo, some of these subjects may have the detoxification capabilities of those rodents in the laboratory, which is an important thing to consider. And that is just due to the deficiency in protein and some key amino acids.

A second thing that we have found out is a key factor for these studies, is that the brain damage that we see -- and this we have learned both from the lab study and human studies -- is not just related for the cyanide intoxication. It is related to cyanide intoxication first, and then also some kind of secondary mechanism, including auxiliary damage or damage of protein by a key metabolite of cyanide, which is known to be a ceramide agent that is cyanate that I see there.

And this makes things very difficult because once you get cyanate in your body, cyanate can modify protein, and you can imagine a compound in your system that can modify protein and eventually even modify the transmission factor and it make up a mess. So that when you study the genetic profile in this subject here, you have to consider the problem not only at the genetic level, but you have to consider the problem at the transmission level at the gene-expression level

[unintelligible], but also at the protein and protein post-modification level.

So, this is something that I just want to mention for you here. And this is also some of the contribution from this work that you get in terms of how large is the impact of our work here. I'm talking about polymorphism on this slide here. We found out for instance that in this subject here, there are very different types of polymorphism, and of course, they become important when they arrive, not very high frequency polymorphisms, for instance. And you will see that we found polymorphisms in our subject not only in the code ingredients, but we also find the polymorphism in regions that initially, many years ago, people thought they were the most important. When you find the polymorphism in untranslated regions, and then it can show here, for instance, here, we found the polymorphisms in this region here, which is [unintelligible] untranslated, which is an important polymorphism that play a role in the stability of [unintelligible] but also in translational control.

This polymorphism here is in the enzyme known as superoxide dismutase, which is an enzyme important for the detoxification or an enzyme that can gain toxicity in the pathogenesis of a disease like amyotrophic lateral sclerosis, which is very similar, but not the same, compared to the Konzo, because it also mostly affect the upper motor neuron disease -- the upper motor neuron system, should I say.

We also found some type of polymorphism, for instance, on this side here that, those polymorphisms are related to the key enzyme that detoxifies cyanide. Those two key enzymes are TSD and NPSD. They are very important polymorphisms in the sense that those polymorphism also play a role in the control, but they also play a role in modulating the localizations of different enzyme within the sets. We show, for instance, that when we have the activity in the brain measured, it's very different than when we have it measured in the spinal cords. So, these are still works in progress. We have some translational aspect of our work. We have some innovative drug delivery system. For instance, we have learned that it's possible by using the toxic properties, like of [unintelligible] toxins, to deliver some peptides directly to the nervous system and be able to circumvent the [unintelligible], which is also very important in terms of translation.

So, we have a kind of work that goes beyond the scope of Fogarty; several institutions or agencies might be involved

including, of course, NIH, with a different institute, but we also have some other type of agency, including the DOD, and that then the [unintelligible] that are also of interest to our subject. So, it's not only research that we conduct; we also do capacity building. And we have built for the purpose of conducting our work, we have built a research unit at the National Institute of Biomedical Research in the Congo that is a complex mobility unit because those diseases, you can't just address them with one single team or with one type of discipline. So you need a multidisciplinary field.

And, for instance -- this is just an example, too. You'd see, this is a subject. So, since we have seen the bottom, a consistent in which the disease cause occurs, we are moving now toward a different type of disease, which is also very complex, which is called Nodding Syndrome. It's an epilepsy-type of disease that is found in southern Uganda -- in Uganda -- not in Uganda, but in Southern Sudan and also another part of the Congo. And you can see, this chart here, eating food, the same type of food, cyanogenic food that you find in those regions, but at the same times they are eating food, but -- and then they start nodding and after a few episodes of nodding, then they may get to grand mal seizures.

And, of course, we also -- we have also been able to build around our complex mobility unit some other type of capabilities. We have a repository; we have samples; we have specimens, DNA serum, plasma. We also get pathogen materials, and we are able to ship it out because we have been able to conduct those studies in the world -- in the U.S. here, but also in the Congo.

We also partner. We establish partnership with other type of organizations, including for instance, a Sudan world that they've donated some sort of mortar for us to be able to built the solar system for the the Suvela [spelled phonetically] system with the villages.

So, I'm going to stop there, and thank you very much. We provide training -- different type of training, one-to-one mentoring, workshop, and then the students come and visit the U.S. laboratories. And, again, as I say, I am very, very thankful to Fogarty, very thankful to NIEHS -- I see my program official there -- very thankful to some of the mentor and many of the mentors I have had during my lifetime, the IBRO people. I've seen -- I don't think she's here -- Professor Marina Bentivoglu [spelled phonetically]. She has been very

instrumental in helping me to get decided what I should be doing for Africa. Hopefully she will be pleased when she will hear about this one. But, otherwise, again, thank you very much, and with all the support of Fogarty, we couldn't do those type of things. Thank you.

[applause]

Kathleen Michel:

We have time for that one question, and if the next panel could assemble over there; Dr. Krotoski will moderate, and Dr. Galler, Dr. Guerrant, and Ryan Hart for Dr. Boothby. Thank you.

So, does anyone have any questions? Gretchen? Oh, and if you have questions, please say your name, and also go to the microphone if you can.

Gretchen Birbeck:

Thank you very much. Thank you, panelists; excellent set of presentations. Apologies for stepping out. Gretchen Birbeck, Malawi, Zambia, University of Rochester, and my question is something of a comment, but also a question for Dr. Hyman, and it might be more open.

I'm struck by your talk, which resonates very much with my own thoughts recently, which is there's been this beautiful body of literature that's come from this very prolific group. And yet, what we have now is a gap between translating that into effective policy, and I also think we're not particularly adept at translating it into an effective interventions -- or interventions that can really be assessed in terms of outcomes and could translate into meaningful policy.

For this brain disorder's program to be so successful, a lot of multidisciplinary silos, kind of things broke down and people worked across disciplines, but now when you think about translating that into policy change, that's a way different -- so how would that -- how do you imagine that translation might occur? Because I think that's really where we're in trouble.

Steven Hyman:

So I think the issue of translating medical discovery into effective treatments for which there's real access, for which there are trained personnel, and for which there's an educated group of people who will be consumers, is very challenging across the entire world. There are special challenges, obviously, in the developing world. I actually think that part

of it, moving from interventions to health systems, and what Jim Kim has called "implementation science," is something that the Fogarty probably is already thinking about -- I would imagine, Roger. But -- and Pamela of course, I was thinking about.

I think this issue about policy makers -- although, you know, I gave you a few speculative slides at the end, it's really something that we have to take seriously. Because if the goal is to publish really good papers and get promoted, then we're doing it. If the goal is to make an impact on human health, then we're not doing nearly as well as we need to, and we really need to thoughtfully come around to what will it take to get to close this gap between what we know and what we do?

Kathleen Michel:

Unfortunately, it's -- Okay, Derek, just one question, then we'll have to close it -- I'm sorry -- for this session, but we can discuss more later.

Male Speaker:

Okay. Well, thanks, and thanks Dr. Hyman for outstanding words. I think the bottom line for me is when you ask the question about the gap between knowledge and action and the unacceptable. It does remind me of the origins of the gap. I think went back to the period at WHO, a decade ago, where we were on the verge of getting mental health to be grasped globally and taken seriously. And then Brand didn't stand for a second term and since then, two directors-general have shown no passion or interest and simply no leadership outside of the worlds of health have stood up and shown leadership.

I do think we're at a new time now, and I'm seeing CEOs and leading politicians, whether it's Patrick Kennedy in this country, or the Deputy Minister in the U.K. starting to speak up. But the one very focused question then is, I have seen -- and now I am working with the opportunity to do things in the workplace, and the employers are saying -- this is a number one or two concern, both from a financial and from a human point of view -- what can we do tomorrow, because we are being told by all the vendors in this country that there's nothing that is -- all the arguments used, and we know that that's not the case. So, I'm just keen to see how you could see the workplace as being the spearhead of actually trying to change the enormous neglect of particularly mental health.

Steven Hyman:

So, the workplace -- there is one very important advantage, which is that effective development of the work force, and especially in the developed world, where the workforce is aging and populations are often declining, the workforce is an important investment. And I think if we can really convince them as they're beginning to wake up to that this goes to their bottom line, they will change.

That said, if I could go back to your earlier comments, I would just point out that in the United States -- we'll leave the developing world out of this, because the United States is such a sterling example -- the Mental Health Parity Act, which suggested that mental disorders and substance use disorders should be treated in the same way as all disorders, passed only because it was the legislative vehicle for the TARP. It was sitting in the Senate, and they needed a legislative vehicle for the bailout bill in the financial meltdown. That passed. It -- the regulations have just issued. So it took five years to issue regulations for the Mental Health Parity Act, even though we have people like Patrick Kennedy out really doing a marvelous job, it doesn't strike me as a priority -- just imagine what AIDS activists would have done during my time at NIH, if a bill that affected their access to healthcare sat around in Health and Human Services for five years waiting for somebody to get to it, to write regulations. So we have a long way to go. But thank you for your comments and questions.

Kathleen Michels:

Thank you very much, and a hand for the panel. Thank you, all of you.

[applause]

IV. Keynote Speakers on the Lifespan Perspective

Kathleen Michels:

And we'll move on to the next panel. Keynotes on the Lifespan Perspective. And if everyone could come up. Yes.

So, yeah if Dr. Weinhardt [spelled phonetically], Dr. Galler, Dr. Guerrant?

Danuta Krotoski:

Well, good morning, everyone. My name is Danuta Kotoski. I'm with the National Institute of Child Health and Human Development, the Unis Kennedy Shriver, the NICHD, and this session entitled, "Keynotes on the Lifespan Perspective,"

highlights the importance of early life experience on individual, physical, and mental health, but also demonstrates that early life exposures can have a legacy that reaches across generations. This will be described by our first speaker, Dr. Janina Galler.

Dr. Galler is the senior scientist at the Judge Baker Children's Center and a Professor of Psychiatry at Harvard Medical School, and she's also the director of the Barbados Nutritional Study that we will hear about this morning. She's received many awards throughout her career, including the first recipient of the Joseph P. Kennedy Jr. Foundation Public Policy Leadership Award in mental retardation. She's a longstanding NICHD grantee, where she's also served as a member of our NICHD National Advisory Council and on the Advisory Committee to the NIH Director. She's a distinguished fellow of the American Psychiatric Association, and has served as an advisor to PAHO, UNICEF, UNPD, and USAID. Today, she will speak to us about the legacy of childhood malnutrition across the lifespan and future generations, in 15 minutes.

[laughter]

**The Legacy of Childhood Malnutrition Across the Lifespan
and Future Generations**

Janina Galler:

I felt when getting up on the stage that I was actually in Sochi. So -- but I'm not. So, I would like to begin my talk by thanking NIH for inviting me to be the first speaker. I've been the recipient at this point of 30 years of uninterrupted support for my work with NIH. My work globally actually antedated the Fogarty Program, but the Fogarty Program has provided fellows who have gone on to do work of their own in developing countries, and the 10th year anniversary which summarizes the intensified focus of this type of support and research, particularly with respect to brain disorders, is entirely important, relevant, and should be a very high priority for public policy.

Malnutrition, which is the area that I work in, is a very prevalent problem across the world. It also impacts not only developing countries, but even in the United States. One out of four children today suffer from hunger on a daily basis. The prevalence of malnutrition has declined certainly over the years, and the millennium goals to decrease malnutrition in the very near future, has had some beneficial impact, but not

sufficient. If you look at the figures, even in 2010, 17.3 percent under the age of 5 growing up in developing countries are exposed and suffer from, under-nutrition.

Speaking in absolute numbers, approximately 183 million children are impacted by stunting, according to a 2007 series of articles in Lancet, and approximately 451 children in this world at the present time are both poor and stunted and not obtaining what they need on a day-to-day basis.

My work in Barbados actually began in the early 70s, but the story goes back to 1966. In 1966, Barbados received independence as a commonwealth nation and at that time, the prime minister declared two major public health problems in the island. One was the very high prevalence of malnutrition, and the second one was developmental disabilities. Dr. Frank Ramsay, a pediatrician on the island, was assigned the task of dealing with the malnutrition problem; Dr. Bertie Graham was assigned the developmental disabilities problem. And, thereupon, he began to systematically document every single child on the island who either had malnutrition or had a risk of developing malnutrition by virtue of being in a family with other children who had malnutrition.

This little research center was actually a building that's approximately a block from the Queen Elizabeth Hospital in Barbados. It formally served as a registrar's home where doctors typically in their residency, in early years of training, would live with their families in order to provide accessible care to the Queen Elizabeth Hospital. We retain control over this building, where we have three little offices and places to have our study participants visit on a daily basis.

One point about Barbados, for those of you who have not been there, it's a small island. It's 15 by 20 miles big only. It is populated by approximately 250,000 individuals, 99 percent of whom are of African origin, mostly from the area of Ghana. And these individuals have lived in Barbados, really from the 1700 and 1800s. Barbados is unique in the sense that it is now defined as number 38 on a list of 187 nations which means that among developing countries it is one of the best and highest developed. And I think you can see here a picture of me -- many years ago of course -- in front of some of the typical homes of children that participated our longitudinal study, and you can see that the population there lives primarily in lower-middle

class homes. They do have a roof over their heads, the kitchen and bathroom facilities typically would be outdoors.

Malnutrition in Barbados, as I indicated before, was quite prevalent in the 1960s and earlier. And in fact, in 1925, Barbados was known as having the highest level of malnutrition and infant mortality anywhere in the developing world. And, as a result, the British government took it upon itself to organize health and educational care, which actually added tremendously to our study because there are very detailed obsessional records of health, of development, of growth, and of educational progress of all of these children.

Malnutrition on the island is similar to malnutrition in other parts of the world. The children are typically, or were typically, exposed to protein shortages and protein energy shortages. And as you can see here, these are two children: the one on the right with Quashiroka [spelled phonetically]; the one on the left with Erasmus. The only difference is that in Barbados, because weaning would occur relatively early, Quashiroka was also seen the first year of life.

One important point about malnutrition on the island, which lead to the ability to do the kind of study that we're doing, is that Frank Ramsay and I worked very hard with the government of Barbados to make malnutrition a reportable disease. So, every single child on the island who had malnutrition obligatorily had to be referred. So we're not dealing with a secondary or tertiary referral system; we're actually dealing with every single child on the island who had this disorder.

Why did children get malnutrition in Barbados? The reason is that this was primarily economic, 8 percent of weekly income goes to the roof over your head and what you eat, so there's very little leeway, particularly in a sugar economy; when sugar markets were low, there was a lot of malnutrition on the island. Also here I quote a very popular Barbadian Calypso song, which also gives the psycho-social construct of this disorder, and it shows that Coo Coo, a common island food, is given to the working man or adult woman who's working. But because the children don't work, they are not the priority.

In our study, we started off with all children on the island who met the following criteria: they were children who had normal birth weights and had malnutrition limited to the first year of life and no evidence of any other encephalopathic or developmental issues. We selected a control group of children

who were neighborhood children, classmates who had no evidence of malnutrition. And, again, because the healthcare system allowed us to have developmental records, all children on the island walk around with what's called a green card. And the green card shows all the immunizations you've gotten, all your health and growth visits. All of these children have documentation from birth and from before birth in terms of what their health status is. So, we were able to have a matched group of kids, and over the years, have added grandmothers, have added other family members. We are actually following about 1,162 individuals and their families in the Barbados Nutrition Study.

Importantly, every one of the children in our program who we followed in our study, had an intervention -- and I really want to emphasize this. These kids, at the time that they were identified as being malnourished, were put into a comprehensive nutritional intervention program at our center, which provided subsidized food, medical care, growth monitoring, and enrichment to 12 years of age. These are not just kids who were followed because they had malnutrition. They were intervened.

And here is the research design of our overall study, and I think what you can see here is the comprehensive nature of the kind of assessments that we did. We looked at each point -- each of these grey blocks represents points -- and the initial red block when we have very comprehensive data on the population for 47 years now, and on a group of intergenerational individuals. But we have looked consistently, partially because of my training in child psychiatry and in mental health, we have extensive behavioral and mental health outcomes, cognitive functions, health, and nutrition. But importantly, we also understood from the very beginning that malnutrition in children, even in developing countries is, in the context of poverty, we documented carefully the home environment, including such measures such as maternal depression, which we measured regularly and consistently at each time point.

This is a very quick overview of basically 40 years of data collection in this population, and I would like to point out a few things on this slide which summarizes our major findings. First of all, the brain and behavior are more sensitive, at least in the early childhood years, than any other organ system, to the effects of childhood malnutrition limited to the first year of life. But, by far and away, our children had much more striking behavioral and mental health disorders than anything else, and by the age of 12 and 13, they had caught up completely

in physical growth and did not show any evidence of any kind of repeat episodes or continuing exposure to growth stunting. Nevertheless, they had many problems. I would also like to point out that many of these problems not only persisted and were able to be documented in a different form at 40, but by age 40, medical problems began to emerge in these individuals as shown by the increased obesity, metabolic syndrome, cardiovascular disease with a 2.7-fold increased risk because of the early exposure.

The major point here in terms of the behavioral outcomes refers to one of the earlier speakers talking about the importance of attention deficits. We had a four-fold increase in early childhood. In 1983, we were the first study to talk about attention deficits in the developing world and particularly in relationship to early childhood malnutrition. Correctly for all sorts of other environmental and home variables, we were able to demonstrate that 60 percent -- a full 60 percent of the children in our cohort, in fact, were impacted by attention deficits compared to 15 percent of the controlled population which at that time compared relatively favorably even with U.S. statistics which showed about 10 percent of kids with attention deficits. These attention deficits have persisted, as I'll show you in a moment.

We also reported conduct problems and in adulthood, most recently the other very, very striking finding which are maladaptive personality traits, personality disorders particularly in the Cluster-A categories -- schizoid withdrawn individuals otherwise very lovely -- and also one-third of individuals have alcoholism, so addiction is an emerging involving mental health disorder in this population. So I want to emphasize those two and also emphasize the comprehensive of the neuropsychological testing that we've also done in this population and we have demonstrated not just IQ differences, which I will comment on in a few minutes, but also cognitive inflexibility.

So, what's the important point here? The important point is one that was also discussed certainly by Dr. Hyman earlier: the incredible social burden of these problems. We reported recently that at age 40, there is clear-cut evidence of increasing decline in educational and occupational opportunities and social status of these individuals who were intervened with and had a limited episode of malnutrition in the first year of life. You can see that by age 40, there is a huge difference in the social status of these individuals who were exposed to early

childhood malnutrition. And I can tell you that we have also looked carefully at the particular pathway that gets these children there, and attention deficits at age five in this population predict a performance on a national 11-plus examination which is a high school entrance examination. The kids do not do as well; they do not get into college, university, focus kinds of programs. And this has a major effect in terms of their life-long ability and educational opportunities. But it all goes back to the fact that that early exposure and conditions surrounding the early malnutrition episode early in life are very pertinent.

What are we doing now? We are currently with NIH support looking at intergenerational outcomes, and I will report a little bit of our preliminary work there. As you can see, at the present time, we have about 60 percent of our eligible population that we are still following 45 years after the initial episode. We actually know where 99 percent of our population still is, which is amazing. About 54 individuals have relocated to Canada, U.K., United States, and elsewhere, but they do occasionally come back to the island and we are working hard to try to identify these individuals as well. We also have a total at the moment of about 100 G-2s and we also have all of our G-0s, the mothers of our original G-1 individuals. And we have, at this point, actually as of late last night, 54 independent families and to show you one outcome trans-generationally attention deficits. These are our key findings at age 40, and what you can see here is the significant difference upon one out of about five different tests of attention deficits. This is the cars and what you see here is that there are striking differences between the previously malnourished and control groups on all areas, particularly inattention; not so much on hyperactivity.

And this is what I call my New York City skyline slide. It shows the second generation behind the first generation and what you can see is that even though the overall scores are higher in the second generation, these were individuals who were 18 to 24 years of age when tested. The pattern is virtually identical with one exception, which is the fact that hyperactivity now becomes much more prominent. And this is a within-family analysis, which basically shows similar findings. It really shows that there is no difference in the two generations. Generation-1 and Generation-2 both show effects of the early exposure of the parent to malnutrition; the effects seem to be persisting in the next generation. And that is a pattern that we continue to show not only with respect to attention deficits,

but also with respect to personality traits on the NEO, which is a collaborative work by Paul Costa and myself and several other behavioral and cognitive parameters.

To add to this, we have also in our laboratory worked from the bench to the human population by in parallel examining the effects in rat models of intergenerational protein malnutrition, specifically on the brain. And I would like to here emphasize the fact that what is really important in our work is the whole concept of critical periods of development. Now, when you look at the rat and you look at the human, obviously there are different periods of rapid growth of the brain. Much more post-natal in the rat, but nevertheless corresponding to the second trimester of pregnancy all the way to two years of age. What we are saying both from our rat work and also from our human studies in the Barbados is that exposure to a limited period of malnutrition, certainly any time in this critical period, not only prenatally, not only as a determinant with low birth weight and prenatal exposure, but any time during that critical period of development has an impact on brain behavior, cognition, emotional expression, and mental health in these individuals.

What we are working on right now is -- are looking at why there are antigen rational effects of malnutrition. We have documented in our animal models that these effects can persist up to three to four generations. Girls respond - the girl rats respond a little bit more quickly than the male rats, but never the less it can take up to four generations for behavioral deficits to reverse themselves.

We have spent a lot of time looking at parenting, socioeconomic factors; we are also currently looking at various medical factors that may explain the intergenerational transmission. But our major focus at the present time are epigenetic changes that potentially impact the next generation. You've heard a little bit about genetics and epigenetics earlier today, but basically these are stable alterations in gene expression during development. And without changing the primary genetic sequences that may have major effects in explaining early exposures and early malnutrition deficits in terms of later outcomes. The Dutch famine study -- which of course is a prenatal exposure, but occurred not in a developing country and occurred in a famine context -- was one of the earlier studies that actually reported reduced methylation of IGF2 and several other genes many years after the initial exposure. This is a theoretical model of how this all works. Malnutrition, we believe effects epigenetic changes and histone methylation, resulting in altered

gene expression and altered phenotype and ultimately transmission to the next and subsequent generations, all impacted by the environment as well as by the early nutritional experience.

This is a quick slide just showing you how -- you know, looking at rat epigenetic profiles and human profiles actually super impose one another. HOMER1 one happens to be one of the genes that we see as being down regulated. And more recently, here is another slide of some changes that we are reporting in our rat models, and I would like to point out this slide in particular because one of the contributions certainly by our animal work is to highlight the fact that the prefrontal cortex is particularly sensitive to the effect of early malnutrition. I think you can see in A and B, which are two replications in the prefrontal cortex, you do see significant down regulation of this KCMJ3 GIRK1 gene. We don't see any significant changes, however, in hippocampus or the brain stem or basal ganglia in these rat models.

Again, as of 4:00 yesterday afternoon, we got a quick report on impacted loci in our epigenetic work in the Barbados study, and, you know, as would be expected, we have multiple changes and multiple overlapping changes in the first two generations. Approximately in first generation about 62 loci being impacted and a similar number in the second generation.

So to give you a quick overview of the legacy of childhood malnutrition and its impact. First of all, I feel that the major contribution that Frank Ramsay and myself and now Sarah Lee Bryce have made to this field is that we eliminated malnutrition from Barbados by 1980. Beginning with our work starting -- my participation which began in 1973, Frank Ramsay's which began in 1966 -- this has probably been our major contribution. Our study has shown lifespan and intergenerational effects on behavior and cognitive outcomes in particular, but also in other health outcomes. There is a major impact on society, a decline in earning potential. And we have also gathered parallel extensive translational studies in wraps, which have examined the biological and social mechanisms underlying the intergenerational effects. And finally our current studies on epigenetic changes may identify new strategies.

This is an overview of our work. And we show that poverty leads to malnutrition with an increased risk of school failure, and this is a vicious cycle. Our current work hopefully will begin

to identify new critical windows of opportunity to be able to enact not just an understanding of what the impact of early malnutrition is about over the lifespan, but also to begin to open new windows of opportunity for interventions. And I would also like to point out that the primary goal in looking at malnutrition and its effects on the brain is of course prevention, early prevention, looking at ways in which -- as Dr. Guerrant will talk about -- ways in which we begin to now understand how malnutrition effects young children in the process of being malnourished, but the important point is trying to break this vicious cycle and to create a legacy of happy, healthy, and mentally healthy offspring.

Thank you, and I would particularly like to thank the NIH for its 30 years of consistent support for the nutrition program at NICHD, and for everyone who has helped us to stay alive these 47 years, and hopefully to make a contribution that will make the lives of children better in this world. Thank you.

[applause]

Danuta Krotoski:

We'll take questions at the end of this session. Our next speaker is Dr. Richard Guerrant, who has focused his research on the effects and potential solutions for diarrhea and enteric infections. And with his colleagues in Brazil, will be discussing today the long-term physical and cognitive development of malnourished children. He is a past President of the American Society of Tropical Medicine and Hygiene and received their Walter Reed medal. He was also elected to the Institute of Medicine at the National Academy of Sciences and chaired the board on global health from 2006 to 2013. Dr. Guerrant received his M.D. at the University of Virginia where he returned to found and currently direct the University Center for Global Health. And today, he will share with us the lessons learned on brain disorders from children in Brazil. Dr. Guerrant.

This is Dr. Guerrant. Could you do the second talk rather than the third on the screen? Thank you. No? Let's see.

Richard Guerrant:

I did get it onto Dropbox, but I don't see it.

Danuta Krotoski:

Is it in here? Could you check and see?

Richard Guerrant:

It was not on the lists that I was seeing.

Danuta Krotoski:

It's not on the list.

Well maybe that's what we'll do. Okay, there are two Rinehartds. Okay. Why don't we go ahead -- no, we want Dr. Guerrant with the G-U-E-R-R-A-N-T. What we may do in the interest of time is move to our third speaker and we'll come back to Dr. Guerrant, and that is Dr. Richard Rinehardt:, who is a Global Health Fellow and Senior Technical Advisor on monitoring evaluation in evidence based practices at the USAID Center on Excellence on children and adversity in Washington, D.C. He is responsible for moving the measurement agenda forward for the U.S. Action Plan on Children in Adversity that was released last year, previously was an epidemiologist with the U.S. Department of Labor and Senior Service Fellow at the CDC. He has a doctorate from the Harvard school of Public Health and has lived and worked in the Philippines, India, and Egypt. And today he'll discuss the USG Action Plan on Children in Adversity and its framework for international assistance. And if we could please have Dr. -- Let's see. Guess what, we're going back to Brazil. Okay. Dr. Guerrant. So I won't have to introduce Dr. Rinehardt, right? You don't mind. Okay, we're back to Brazil. Thank you. All right. Hopefully they won't count that off your time.

Lessons about the Brain from Children in Brazil

Richard Guerrant:

That's great. Thank you so much. I'm delighted to see that I actually do exist, so thank you.

This is an incredibly special opportunity to present at this group. It's a little bit intimidating because so many of you are brilliant leading neuroscientists, and I'm just a diarrhea doc.

[laughter]

But I always learn more than anybody else at these things, so let me share what we are struggling through and learning.

This is actually my -- also my acknowledgment slide after my marathon. And right here the key person who really is doing an awful lot of this APOE work is Renaldo Oria, who's sitting right

over here. And we have incredible collaborators over many years, Aldo Lima at the Federal University of Ceara in the northeast of Brazil; Rebecca Scharf is here teaching me about developmental pediatrics. And we have been incredibly fortunate over an extended period of time to have the support of the Fogarty Center, the training programs that are APOE studies have been tremendously supported by this program, and over many years now our citer award as well with NIAID. We also are now privileged to be working with colleagues at the University of Redding, who are in metabolomics. Metabonomics, I'm being taught, is when the whole organism can be assessed. But let me just thank you for this opportunity. And what I would like to do in my 15 minutes is really focus on three messages.

The first, that early life diarrhea illnesses and enteropathy, perhaps even without overt squirts can stunt, literally, in just the first two years of life. Those early enteric infections may stunt as much as eight centimeters of growth by the time a child is seven and as much as 10 IQ points. That this actually may also associate with later life obesity -- metabolic syndrome, as Dr. Galler has already introduced. That this IQ decrement, the cognitive hit, is actually, at least to my simplistic notion, a bit like the Alzheimer's deficit. And I'll mention that a little bit more because that's why we started looking at this crazy -- I wasn't smoking anything, Roger. It was because of the nature of that deficit that we started looking at APOE, and we were 180 degrees wrong. There is an association, but it's protective, not worse.

In fact, now I'm trying to understand what this really could mean. Is it possible that diarrhea or enteropathy is what, at least in part, might make senescence an adaptive trait? I'm going to have to think a lot longer about that one.

And then I'll try to get into at least the beginnings of where we are now, starting to look at genetic and metabolic tools to understand not only the mechanisms and hopefully biomarkers, but even to direct the development of interventions. Now, I'm not an avid reader of "The Economist," but it came to my attention from colleagues who are better than I on this that Christopher Eppig's paper now three-and-a-half years ago was picked up by "The Economist" describing how the Flynn Effect -- I didn't know what that was either -- but the association of improving IQ with development is in fact not because of malnutrition. [laughs] Sorry. And for us or poverty, but in fact was infectious diseases. Now there's, I'm sure, controversy around this but this was even when controlling for GDP per capita education,

nutritional deficiencies per say, but in effect, though, it helps set up our major interest in this vicious cycle, which is going to, in a moment, look a great deal more like Dr. Galler's vicious cycle. And that is that enteric infections with or without overt squirts -- a bizarre cultural notion of a disease -- through this alteration and inflammatory signaling pathways absorptive function leads to impaired growth and development. And that furthermore, malnourished children get far worse, more frequent, and more prolonged enteric infections. That can be shown in the field; it can be shown in experimental models that this vicious cycle is clearly going on.

If those -- now the good news is that the number of children who are dying from overt diarrhea, thanks to ORT, and we still have a lot of work to do on that, but it has come way down. It may be coming under 7 million a year now, for the first time in a very long time. It was much -- three or four times that. However, the number of children who are malnourished, where they're stunted or wasted or some combination, are well in excess of 170. I think your figure was 183 million. That's one in every three to five children in the most populous countries around the world. So that's a huge decrement if you translate that to a 10 IQ point decrement.

In addition, there may actually be an independent effect of these infections on cognitive development. That's a bit more controversial. In addition to the effect through stunting, and of course there are interventions that I would argue we have to do in combination if we're going to really make that difference that we seek to do. But these are clearly also potentially interacting with other non-communicable diseases. Heart disease, cancer, strokes, metabolic syndrome; obviously there, healthcare budgets and contributions to poverty making a very similar vicious cycle to the one that Dr. Galler just showed.

So our interest is in taking a child who, like Leonardo Monta showed, does remarkably well for a few months until they're weaned and start experiencing all of the gut infections and other infections that literally pull them off the growth curve. How can we take a child who's starting to fall and get them back up? There is catch up growth, if there's not a lot more diarrhea. I won't belabor the data on that, but it's very clear and in fact there is, even as catch up, signaling through intestinal cell cyanates. It's fascinating in terms of a child getting back as opposed to continuing on the same curve, or, worst of all, just continuing to be pulled off by these repeated illnesses.

So what we're talking about here is something -- it's difficult to biopsy malnourished children, but John Lindenbaum was able in the 60s to biopsy Peace Corps volunteers. Now Peace Corps volunteers often lose a lot. I won't ask for a show of hands in this room, but I'll bet we could, and there's often weight loss not because you don't eat, but because your gut has lost this incredible tennis court surface area that is renewed every three days by these Crypto. cells dividing and multiplying and migrating up to become absorptive villus epithelial cells, completely different cells than apoptosis intraluminal. They're wiped out. And there's a striking inflammatory process in the lamina propria. I believe that both of those are likely to be very important to diarrhea stunting development, and perhaps even the brain development. That's the focus of this meeting.

Whether we can learn enough to begin to appreciate potential interventions are really critical questions that we must address. So if we start to tape together the growth impact fitness cognitive impact that has been -- that we mentioned and even delay of 12 months of school performance, just attributable to the first two years of enteric infections, you can easily double -- frankly it's a five or six-fold increase in the DALY value of an intervention. If we can make a difference. Salazar Victora has called this height at the second birth date the most -- the best predictor of any of what he calls human capital, or human -- humanity itself. One can even take specific etiologic agents, specific pathogens and find data for these various impairments. And there are many other references than just these here that will clearly show that.

But let me drill down of that cognitive impairment for a moment, the topic of this course, because here is the nonverbal intelligence scores on these tests. One of our students was down there working on this. His Portuguese wasn't much better than mine, but this was nonverbal intelligence. You can see how this precious little girl could pick which belongs here, and you can quickly tell me which of these belongs here. I'm sorry, your time is up. It's a very good test, and some of the smartest people missed it in our lab. And that's the relationship of diarrhea in the first two years of life with those TONY test of non-verbal intelligence scores, and that's where you can easily get a 10 IQ point decrement with just that first average diarrhea burden.

Furthermore, I had to start learning about which kinds of fluency testing we were doing and learning about. And it was

predominantly semantic more than frenetic fluency. Now, what is that? I'm a simple-minded guy. So you ask a child to name as many fruits or animals that they can in a minute. Let alone they're Brazilian kids; they know more fruits and animals than we do, but they're compared with each other. That is retrieval from another brain region as opposed to phonetic fluency, which is simply a rote memory, if I could use that term, which is as many -- name as many words that begin with a consonant sound, which is not as complex as a retrieval process.

And it turns out that unlike Parkinson's dementia, which I understand may affect both, that Alzheimer's tends to effect predominantly the semantic fluency and retrieval from another brain region. What is a fruit, what is an animal, and then name it. Now any of us who has the good fortune of loved ones and those near and dear to use living long enough knows this horrible disease of Alzheimer's disease. And my dear mother died in her late 80s with Alzheimer's. And she had been quite an accomplished pianist, able to play remarkably beautifully long after she was quite sure who I was. And that's sort of sad in an elderly lady; that's horrific in a child for a lifetime. That's what we're talking about.

So that's why we looked at this APOE-4 gene. They're bound to be worse, right? Wrong. They were protected. They were not only protected from some of the diarrhea, but the protection of the cognitive hit was only in the children that were getting heavy, heavy diarrhea burden hits. Here's that -- your slide, Dr. Galler, about the human brain development. This shouldn't be a big surprise. When's the last time you saw a newborn human infant. This little -- I sometimes get in trouble. This little creature sort of lies there, makes a bit of a mess, a bit of a racket, but does very little else. And yet, within two years, this little creature walks, talks, and has personality about like it's going to be; I hate to have to remind you. And it turns out that unlike some other species -- I'm surprised; there are apparently primates over here that come out pretty well at birth. Guinea pigs are really fantastic -- hold it, giraffes, horses, gazelles may outrun their moms in two or three days -- not a human. And whether you look at brain weight or synapse formation, look at this. This is our synapses at birth. Hello, by two years, we peak. After that, we trim. I understand we might be able to make a few more, but we lose more -- anyway. It's -- We -- anybody over two has peaked and here is where the legions are. I'm not even a pediatrician; I'm an internist, but I have to admit that this is where the action is. Why? Because that's when the synaptic tracks are formed and that's

also the time at which a child is most vulnerable to these repeated infections.

Now I've mentioned not only this effect on stunting and cognition -- perhaps even a direct effect -- but what if stunted children are a greater risk for obesity or metabolic syndrome? Or there is even a direct effect. And each of these arrows has -- I'm sorry that nature took out all my little references, but they're in the paper. But Mark Dabur [spelled phonetically] has reanalyzed some of the data from Mark Derrell [spelled phonetically] and the early Guatemala studies, and sure enough it looks as though there may be a direct effect there. Through what other signaling pathways that are so important to begin to understand, perhaps pro-inflammatory processes.

Suffice to say, though, that it is arguably as important even to Ledweena [spelled phonetically], the mom of these three children. One of four children, actually; one of whom she lost to a diarrheal illness in the first year of life. When we started our studies, we learned about that. And yet it may be almost as important even to her, the other three that didn't die but that lived through repeated malnourishing diarrheal illnesses in this critical formative period of life.

So what are the -- how do we tell which child is in trouble? What's going on? Well, here's where this collaboration with Johnathan Swann at University of Redding is fascinating because in Aldo's malnourished children already in the preliminary analysis, we're already seeing this dimethylamine pathway that I'll come to in the next slide, a signal here that suggests inflammatory processes in the urine of malnourished, as opposed to better nourished children. And in methyl nicotinic acid and methylnicotinamide, which are two of the markers that we're up in the children with -- who are destined to come down with autism. So a fascinating story that in fact, John Swann can also help confirm in our mouse models. Here with malnourished mice having more of that trimethylamine choline pathway. Infection driving the trimethylamine oxide -- did I get credit for my first -- I'll get going quickly. And then this being an APOE-dependent pathway, which is fascinating because Stan Hazen has come along right after we started seeing these data, and said guess what. This phosphatidyl choline pathway from all the red meat carotene and egg yolk lecithin that we eat gets to our gut and probably with some specificity our flora, chew it down to choline and trimethylamine. That trimethylamine is converted by hepatic Flavin monooxygenases to this trimethylamine oxide which is associated with heart attacks, strokes, and death.

Roger, we want you to defend the non-communicable from the communicable diseases because malnutrition drives up TMA. Cryptosporidial infections drive it to the TMAO, and it's an APOE-dependent enzyme that is in fact connecting those two.

We're also getting into GWAS on now over 1,400 children, but let me wrap up with an animal model of two infections while not getting to our C-inf story with agent mice that we think may be hugely relevant to 40 percent of nursing home residents who have inflammatory evidence of inflammation in their stool studies; that's another day, but let me focus on cryptosporidium and enteroaggregative E. coli. Crypto because it is clear that the vicious cycle can show that infection reduces growth, infection - malnourished mice further impacts their growth and the malnourished mice shed more so that's the vicious cycle. In case there's any doubt, here's malnutrition, here's infection and the two in combination. I mean, this is not subtle.

It's in that setting that Carol Colton has taught us that the APOE-4 gene, when put into targeted transgenic mice, in fact up regulates an arginine selective transporter. Guess what? Arginine in our best anti-cryptosporidial drug, acting to knock down crypto not only lame-dependent, but also by the arginine's dependent pathway. And finally we can complete the cycle by showing that the targeted transgenic mice in fact grow better and have better histology and get rid of the parasite better.

So we think we may be starting to close that gap. The same picture can be shown for the enteroaggregative E. coli bacteria, but I want to mention that because zinc not only affects the organism and its virulence traits, but also the host of course. And, in fact, zinc deficiency increases the valence of the organism, as well as the damage or disease with the host. And that's of tremendous importance because we can take a mouse with either zinc or protein deficiency only and see a specific up regulation of meningeal M1 macrophage activation. In the meninges, not in the spleen, not in the lymph nodes, but in the meninges. Perhaps related to disrupted tight junctions and circulating LPS responses.

I'm afraid time won't permit my telling an extraordinary story of Jana, who's a beautiful little girl who struggled with some of her tests, drew the most magnificent picture, but without hands signifying that she in fact any sense of empowerment to deal with her lot in this world. Roger, this is why we have to be involved. That's who we are.

Sunrise on the Amazon. We have a dream to start doing the doable. What can we do about this? Well, you know, there are a few little promising pieces on the horizon. Reynaldo showed that zinc and glutamine can improve hippocampal architecture and synaptic genesis. And indeed in the children there may even be a clue that zinc, glutamine, perhaps with Vitamin A also, can improve their verbal learning skills in these children with the predominate effect being gender specific in the girls more than the boys.

So, my concluding slide then is back to the summaries of early life diarrheal illnesses having a profound effect not only on growth but cognitive development and perhaps later-life problems in non-communicable diseases, Alzheimer-like deficit but APOE is protective and may give us some clues about our own evolution, as well as clues about what to do about this mechanisms bio markers and interventions. But the real reason that we are here is because of these children and what it is that they are meaning to all of us, because how they do is what determines how we will do. Thank you and I appreciate your time.

[applause]

U.S.G. Action Plan on Children in Adversity

Danuta Krotoski:

Great. And now hopefully we'll get the slides for Dr. Rinehardt who's already been introduced to you. So, he will speak to us about the U.S. government action plan on children in adversity. Thank you.

Richard Rinehardt:

Great. Thank you for the opportunity to be here. And I have to say on the agenda you probably noticed that I'm filling in for Dr. Neil Boothby who regrets he can't be here. And I don't -- for any of you who know Neil Boothby those are some pretty tough shoes to follow. So, I'll try to do my best.

And I guess while we're getting the presentation loaded up here and -- yeah, that's the right one. I have a question to people in the audience, maybe just a quick raise of hands. Has any ever heard of the U.S. Government Action Plan on Children in Adversity? All right, we have a few people. So, by the end of my presentation everyone will raise their hand.

[laughter]

So, that'll be a test. But I think this is really a good example of a lot the good you've been doing on the science and evidence, and it's evolved into policy. And this is a U.S. government action plan. It's a strategic framework for international assistance. It was created by seven different agencies and departments, including the NIH was very active in it. We came together when we put together this strategic framework, and it was launched at the White House last December or December 2012, and we also have a website.

Okay. And so -- I guess I just wanted to point out the sort of precursor and what really motivated the U.S. government to create this action plan was that in December 2011 there was a Major Evidence Summit on Children Outside of Family Care. We had about 150 people from academia, practitioners, implementers, and from the government. Massive numbers, thousands of articles were reviewed, and it ended up we had seven papers that were put together. We had a special issue in the "Child Abuse and Neglect: The International Journal" that came out in November 2012. But, one of the key things with this evidence summit was that there was a commentary in the Lancet signed by 10 senior leaders in the U.S. government that said within one year, we will create a strategy to address these children's issues.

And so, I just want to say if you want to see sort of evidence go into action into policy, you have to get 10 senior leaders across the U.S. government to say we're going to do it. And, that's really what pulled everyone together to do it. So I have a quick video, and I think this is probably going to be very basic, and I think it says the same thing that has been said, but I'd like to play it. It's just a minute, minute and a half, and it really covers -- well, it's been very powerful for us and it resonates with decision makers, policy makers, not just here but also in developing countries. So, I'm not sure how to play the video.

Danuta Krotoski:
Do you just need to click on this?

Richard Rinehartd:
I don't know.

Danuta Krotoski:
That's why it's not an Apple.

Richard Rinehartd:
Oh, here we go.

[video begins]

Male Speaker:

A child's experiences during the earliest years of life have a lasting impact on the architecture of the developing brain. Genes provide the basic blueprint, but experiences shape the process that determines whether a child's brain will provide a strong or weak foundation for all future learning, behavior, and health.

During this important period of brain development, billions of brain cells called neurons send electrical signals to communicate with each other. These connections form circuits that become the basic foundation of brain architecture. Circuits and connections proliferate at a rapid pace, and are reinforced through repeated use. Our experiences and environment dictate which circuits and connections get more use. Connections that are used more grow stronger and more permanent. Meanwhile, connections that are used less fade away through a normal process called "pruning." Well-used circuits create lightning fast pathways for neural signals to travel across regions of the brain. Simple circuits form first providing a foundation for more complex circuits to build on later.

Through this process, neurons form strong circuits and connections for emotions, motor skills, behavioral control, logic, language, and memory during the early critical period of development. With repeated use, these circuits become more efficient and connect to other areas of the brain more rapidly. While they originate in specific areas of the brain, the circuits are interconnected. You can't have one type of skill without the others to support it. Like building a house, everything is connected, and what comes first forms a foundation for all that comes later.

[video ends]

Richard Rinehardt:

Okay. Great. And I should just point out that this video, and I have another one that's going to come right after it. It was developed by the Harvard Center on the Developing Child. And I realize this is, you know, I guess Brain Science 101 for all of you here, but this kind of information has been very powerful in the policy world in helping us to really get things going.

So, what do we mean by adversity? We say children in adversity. If you think of low and middle-income countries, there's about two billion children in low and middle income countries. About a quarter of them live in extreme poverty. And I think what we're talking -- or how adversity is defined are essentially those children but with other bad things happening. Whether they're living outside of family care, poor health and nutrition, and we've heard a lot about, you know, some of these effects on children. Exposure to violence, abuse and neglect. So what we're saying is that adversity is serious deprivation or danger.

And this is a slide, I think we've equivalent slides to this earlier, you know, it just shows that, you know, it's as particularly in the early years more sophisticated steps occur building on, you know, sort of basic things in our development.

And what I want to show is one more slide, very brief. And this is also developed by Harvard, but it's what happens when I think things go wrong.

[video begins]

Male Speaker:

Learning to deal with stress is an important part of healthy development. When experiencing stress, the stress response system is activated. The body and brain go on alert. There's an adrenaline rush, increased heart rate, and an increase in stress hormone levels.

When the stress is relieved after a short time, or a young child receives support from caring adults, the stress response winds down and the body quickly returns to normal. In severe situations, such as on-going abuse and neglect where there's no caring adult to act as a buffer against the stress, the stress response stays activated. Even when there is no apparent physical harm, the extended absence of response from adults can activate the stress response system.

Constant activation of the stress response overloads developing systems with serious life-long consequences for the child. This is known as toxic stress. Over time, this results in a stress response system set permanently on high alert.

In the areas of the brain dedicated to learning and reasoning, the neural connections that comprise brain architecture are weaker and fewer in number. Science shows that the prolonged

activation of stress hormones in early childhood can actually reduce neural connections in these important areas of the brain at just the time when they should be growing new ones.

Toxic stress can be avoided if we ensure that the environments in which children grow and develop are nurturing, stable, and engaging.

[video ends]

Richard Rinehardt:

Okay. So, back to the U.S. Government Action Plan on Children in Adversity and how it's framed. It essentially has six objectives: three principle objectives and three supporting objectives. And for the principle objectives, you know, the action plan is saying if invest in these three things, we can do good things for kids. And then what I want to do for the, just the remainder of my presentation is just kind of briefly go through the three principle objectives, but then also end up on the fifth objective: promote the evidence-based because I think that's very relevant to the meeting today.

So, build strong beginnings, objective one. In -- so, I work, I'm a Global Health Fellow. I work in the global health bureau at USAID, and there's a huge emphasis at USAID, the U.S. government, and globally on child survival, and I think a lot of us, you know, have seen the statistic 6.9 million children die before the age of five worldwide. But what's not talked about often, at least in the development community, and I have heard it alluded to today, is that about 25 times that number, over 200 million children are expected to live past five, but they're not expected to reach their developmental potential. And this is a huge burden on societies, and there's been estimates of 20percent loss in adult productivity. And there's also a lot of data. There are evidence that suggests that the more risk factors that children have at an early towards adversities end up with more developmental delays.

This is a study that -- I think it played a big part in objective one. It's a randomized control study from Jamaica. Some of you are probably familiar with it, but it look at kids who are stunted, and it really it shows all good things. It says that with kids who are stunted, if you give them nutrition and supplements only over time, they -- their IQ or developmental quotient increases. If you give them early stimulation with caregivers and parents over time that that also increases. But what it also says, and it's this red line, is

that if you combine those two in more of an integrative, holistic package, that the stunted kids over a two-year period are almost reaching the levels of this developmental quotient as the control group.

Put family care first. This really focuses on children outside of family care. There's wild estimates of how many kids in institutions and orphanages; most countries do not know how many kids are in orphanages. Street children or kids associated with the street, those numbers are very difficult to come by. One of the challenges with, you know, quote, "children outside of family care" is that most of our studies and data that we have on children at least prevalent studies, national studies, are based on household-based surveys. So, by definition, you know, there're going to be missing this area of children outside of family care.

You may also be familiar with the Bucharest study which, you know, looked at the -- sort of the impact of institutionalization on children, and in what this study showed, there was a group of children in institutions, in orphanages who had an average IQ of, I believe it was around 64. And in children in the neighborhoods, in the communities near the institutions had an average IQ of 103. And when the children from the institutions were removed before the age of two, integrated in protective, caring, and loving families, that over two or three years, they -- I think their IQ went up into the high 90s, you know, very close to the control group. But when they were removed from institutions after age two, their IQs never got above the high 70s or 80s.

And so there's a lot of effort and issues going on with children in institutions, and I mean we could go on that for a long -- a different conversation, I guess.

Children, objective three, protect children from violence, exploitation, abuse, neglect. There are -- I mean, it's essentially an epidemic. The CDC has been doing these violence against children surveys in many African countries, and they're starting to do some in Asian countries, which is looking at national prevalence of boys and girls emotional, physical, and sexual violence, and the numbers are staggering. And where violence occurs; it occurs in schools, on the way to schools, in the homes, you know. Those kinds of things have really sparked a lot of government action to address some of these issues. Hazardous work, hazardous child labors is a big issue as well.

This is a slide; it's probably one of the best studies. It's an early study, the ACE study, the adverse child experiences and it just shows that this sort of, with violence and other adversities that they do have long-term negative effects on people and on societies. So, just to sum up what the Action Plan on Children Adversity says is that if we invest in these three areas, and with children -- well, what it says is if we do three things in priority countries -- reduce the number of children not reaching the growth and developmental milestones, reduce the number of children outside of family care, and reduce violence, exploitation, and abuse -- that these are pathways out of adversity, and that they will do good things, you know, for communities and for societies. So, that's really sort of in a nutshell what the action plan is about.

I wanted to end on this objective five in the action plan, which is promoting the evidence base. And again this is -- it's a U.S. government action plan. NIH is a part of this, you know, other agencies, you know, we have DO, Department of Labor, Department of Agriculture, Peace Corps, State Department, USAID, et cetera. But there's a commitment to fund research to have research driving future policy decisions, and also to, for the U.S. government and also to work with universities overseas. And a lot of, you know, the kinds of things that Fogarty is putting forward. So, that is a big piece of the action plan.

And then, this is my last slide. We are supporting -- we're the -- we're at a planning stage right now of a -- which is going to be a fairly major longitudinal research study on child adversity. And we're, looks like it's going to be taking off initially in Uganda with Makerere University, and there's a new center for the study of the African child at Makerere, and then some other groups are involved, some foundations. But it's really looking at pathways out of adversity, you know, from resilient youth to productive adults. And there's -- I think because of the action plan, there's going to be a lot of emphasis on continuing, you know, the kinds of research that you do, and other things that can lead into better policy, better decision making, better development of programs that, you know, can do good things for kids. So, that's it. Thank you.

[applause]

Danuta Krotoski:

Thank you so much for stepping in for Dr. Boothby really at the last minute. We very much appreciate this. I think we can have time -- I realize that we're into the break.

Kathleen Michels:

I would -- We have a panel of the NIH director's right after the break, and we won't have time for the break, I think, if we have questions. So, hopefully everyone will be around, and we can -- that was a fabulous session. So, if everyone could take 15 minutes. Be back at 11:05 for the NIH director's panel. And I believe there's coffee and tea that you can actually buy out here or up in the cafeteria or snack bar upstairs.

V. NIH Institute Director's Panel: Reflection on the Global Missions of the NIH ICS and their Vision for the Future

Roger Glass:

Okay. Are we ready? I hear a resounding yes. Can I hear a yes?

Audience:

Yes.

Roger Glass:

Okay; that's what we needed. Again, I'm Roger Glass, Director of the Fogarty. Here, we have an absolutely wonderful panel of mostly Institute Directors who have been engaged with this program from the onset. And this is our chance to hear from each of them what they see in this program.

You know, when I began my talk this morning, I said 10 years ago, what were they smoking to decide to engage in this global neurologic health agenda? What did they think at the time? What moved them? Was it money? Was it ethics? Was it discovery? What were the issues that got them engaged? And now, it's 10 years later when we've had an absolutely wonderful program, a trans-NIH program. Probably the most successful trans-NIH program we've had in global health, and this is a chance for them to reflect on what this program has meant to them, how it's expanded their own areas of research. It's provided them an opportunity to think about the vision for neuroscience. As we think globally about the non-communicable disease agenda and to discuss opportunities of going forward. Where do we go from here?

So, with that, I have the panel. I don't have any special order except the order that's in the session. Maybe we'll just go across here, one-by-one. Is that okay? Alan?

We'll start with Alan Guttmacher, Director of the Eunice Kennedy Shiver National Center for Child Health and Human Disabilities. Alan, begin.

Alan Guttmacher:

Thanks Roger. And I won't tell you what we were smoking, but I can tell you that we at NICHD like, I think the other folks up here, having been smoking it for a lot longer than 10 years.

[laughter]

A key part of the mission -- I'll read you part of our mission at NICHD. Part of it says, "To ensure that all children have the chance to achieve their full potential for healthy and productive lives, and to ensure the health, productivity, independence, and well-being of all people through optimal rehabilitation."

When we were -- NICHD was founded by President Kennedy a little bit over 50 years ago. We were really founded around the issue of child development -- that's why it's in our name -- but particularly around the issues of intellectual and developmental disabilities. And in fact that has been part of -- a core part of who we are for the entire period of NICHD's existence, and also we have had a key interest, particularly in this area, but other areas in general, in terms of global health. So, the issue of, you know, global neurohealth is really part of who we are. So I think we have seen this program is yet another way to engage in that.

We have particular interest, of course, in something that's already been referred to today: the first 1,000 days, but so do a lot of other institutes, we're glad to say. But we do feel that, because of the cadre of researchers that identify with NICHD et cetera, this is an area that we've long had particular interest in. And we also, of course, have interest in child development well beyond that. So that we have long been engaged in the question of optimizing not just pre-natal care, not just trying to see that all children globally are born without health or any disability. But also we've been very interested in cognitive development, not just in the first months and even years of life, but well beyond that, and continue to support research that actively explores that.

You'll be glad to know I'm not going to detail all of the efforts of NICHD in this area because I don't have the time for that, and I doubt that you have the patience to hear about all

of it. I would point out a couple things before I detail some of those, and that is I think that now we face a particularly important opportunity in terms of looking at the issues around which this conference and this program is really focused for two reasons. One is that we clearly have better than we've ever had before, better tools for looking at issues of neuro development, and are quickly due to the Brain Initiative and other things that you mentioned that you're going to be hearing more about developing more of those. But also, looking at this from a sort of child development perspective as we are doing a better and better job answering that crucial question of simply child mortality. Not good enough a job, but better and better job doing that globally, and even many of the sort of traditional morbidities of childhood. Then the issues of intellectual developmental disability and [unintelligible] become relatively even more important for us, even beyond the fact that we have new tools for them. Clearly, as I said, NICHD's long been involved in this with NICHD scientists who played a key role, for instance, in developing the HIB vaccine, which has made such an impact in terms of lowering rates of meningitis and its sequellie.

I think -- I know you heard this morning from two NICHD grantees, Drs. Janina Galler and Richard Geurrant who spoke about the importance of nutrition and other early life influences on both life-long health and also cognitive function. And of course, our researchers have shown the impact of nutrition not just on child development, but really on life-long health and development. We're very proud of our biomarkers in nutrition for development or bond program that amongst other foci seeking to identify nutritional biomarkers for neurocognitive development to aid in both research and program development.

The prenatal AIDS, the prenatal alcohol and SIDS and still-growth network is a partnership of several NIH institutes, in which we are very glad to participate. Includes communities in the western cape of South Africa and its investigation of the role of prenatal alcohol exposure and adverse pregnancy outcome in SIDS. Our global network for women and children's health research has a very strong international focus looking at many areas of both pregnancy and early child health that plays an important role. Our pediatric and maternal HIV infectious disease network has done lots of clinical trials and treatment, maternal to child HIV transmission, et cetera, and had helped, I think, in terms of making that much less of a global problem, though it still certainly is one.

We helped support the Minerva Network, an international study design to address the contributions of familial and environmental factors in autism.

Roger Glass:

Alan, let me keep you to five. Keep everyone to five minutes, so we can have a --

Alan Guttmacher:

So, how close am I?

Roger Glass:

You're very close.

[laughter]

Alan Guttmacher:

Okay. So, then -- I was going to talk about the things we were going to do, but you can ask us about that in the panel, right?

Roger Glass:

Yeah.

Alan Guttmacher:

So, why don't I just wrap it up with that and say I hope that I have demonstrated to this small, almost random smattering of things that we've been involved in --

[laughter]

-- that we've long been quite interested in this, and our interest has flagged, but we see this for various reasons as an increasing area of interest for us.

Roger Glass:

Thank you, Alan. Richard of Alzheimer's, aging -- aging is something I hope we are all going to experience. Can you help us through global health research, do it better?

Richard Hodes:

Well, thank you for the chance to talk about it. First, to put in perspective the growing importance of older population globally. A recently as 1950 or so, the proportion of people in the world aged over 65 was at about 5 percent. The proportion of kids under five was about 15 percent. Somewhere in this decade for the first time clearly in human history, there're

going to be equivalent numbers of those over 65 and under five. And those trajectories are going to keep on diverging, so that within the range 2030, 2050, we'll have something like 15 percent of the world's population over 65 and closer to 5 percent under five. No offense.

Alan Guttmacher:

No. We consider that a good thing.

Richard Hodes:

And the challenges here are clearly going to be absolutely enormous. In particular, the challenges posed by age-related diseases. In that regard, the global change is even more impressive than it is in the U.S. where a lot of the population changes I mentioned are going to be occurring in the developing countries of the world. And as a result, I could just outline the areas of research in which international or global perspectives have been critically important.

They started with factors such as looking for genetic risk factors, where in the past years the ability to identify new genetic risk factors has involved collaborations among international groups of investigators could not have been done as otherwise. In the United States, the Health and Retirement Study, which was undertaken to look at risk factors for health, loss, and disability has been a real landmark study, and is all the more important, because it is now global with harmonized studies over the majority of the world's population represented by a now international efforts having begun in this country.

In terms of looking for ways to diagnose and track the course of dementia, and Alzheimer's disease in particular, ADNI, the Alzheimer's Disease Neuroimaging Initiative, began in this country as a public private partnership, which has been widely successful, I would say, in terms of identifying biomarkers for disease. And now, worldwide, ADNI again is covering most of the continents of the world with harmonized importantly means for making data available that are interpretable across the globe and interpretable and accessible to all investigators I think even to the point of clinical trials.

I think you heard this morning a bit about some of the innovative trials going on that are now being targeted to those individuals with the tragic early onset, dominantly inherited Alzheimer's disease. The largest cohort in the world of this is in Columbia and recently in a collaboration in which NIA plays a critical role, studies have began to look at interventions in

that population where it happens that there are parts of the globe where there are populations that are uniquely in need of intervention and informative. There've been international efforts in that regard. So, I hope to have conveyed briefly in the spectrum from looking at populations to genetics to underlying mechanisms to treatment; more and more we've been globally involved.

As recently as December, there was a historic G8 summit on dementia which was looking at the ability to internationally plan for both research as well as social and clinical underpinnings that are demanded by the epidemic of dementia that we have before us. This will be followed by a series of Legacy meetings just about a year from now, probably in this very same room. There's going to be a Legacy meeting sponsored by NIH, NIA, in which following a two-day meeting of experts, we'll have a third day specifically targeted to global investments, collaborations, and coordination of research efforts.

So, from past to that hint of the present continuing trajectory in global diseases, I'll leave you with that summary and be happy to discuss as time allows.

Roger Glass:

Great, Richard. Thank you very much. Next, Story Landis is head of the -- Director of the National Institute of Neurologic Disease and Stroke. Story.

Story Landis:

So, we have embraced the brain disorders in developing countries initiatives that Fogarty has spearheaded. I know you heard this morning about the burden of mental illness. The burden of neurologic disorders is equally devastating, and in fact often not acknowledged the way it should be because it gets packaged under mental illness by World Health Organization.

I want to give you several examples of, I think, really extraordinarily successful programs that we've started in the Fogarty initiative and then that have developed independently. They all focus on epilepsy. You know, epilepsy in this country is prevalent, but for two-thirds of the patients, there's -- well, there's good control either because of pharmacological treatments or surgery. But in Africa, for example, there's a higher incidence because of issues with child birth, and there is almost no recognition of this as a medical disorder. Oftentimes, it can be thought of as possession, and medications are -- that would be freely available in this country, older

medications are oftentimes not available in Africa. So, very big burden.

We funded Gretchen Birbeck, who is from the Midwest but has run a program in Zambia for a number of years. She spent six months in Zambia and six months in Michigan, and her principle research focus has been on reducing stigma, getting people to understand that this is in fact not possession, but a treatable neurological disorder. And she's been addressing this problem in two different ways. First, running a clinic, which has been extraordinarily successful, but also at the societal level and trying to develop programs that will increase access to care, getting kids and mothers and families to recognize that they can get treatment.

A second example of an effort in epilepsy is a clinical trial that we've been running in Peru run by a Dr. Garcia, and this has addressed the issue of neurocysticercosis. This is a form of epilepsy caused by cysts that form in the brain from pork tapeworm. Very bad. It turns out that one-third of the patients in the U.S. who come into a public hospital in Houston, Texas -- Ben Taub -- who have epilepsy actually have epilepsy caused by neurocysticercosis. So, it's not just a developing country issue; it's also an issue in this country. And he has run a wonderful clinical trial that's looked at the effects of doing away -- ablating the cysts caused by the tape worm in the brain and has shown that -- trial was stopped early, because it became very clear that seizure incidence significantly increased if you got rid of the cysts which cause inflammation which then cause epilepsy.

The third that I want to highlight very briefly is work that was started with an R21 from this program done by Ben Warf, who I've heard is going to be speaking later, a neurosurgeon. He established a neurosurgical program in Uganda and has worked on developing an alternative for shunts. Now hydrocephalus in this country is treated with shunt implantation. The shunts often need to be changed, cleaned, infections can arise, and that's obviously not a technology that is useful in Africa. And Ben has worked out an alternative strategy which is as effective or more effective and is actually -- makes a huge difference.

So, several examples as NINDS looks to the future. In addition to these specific initiatives, we're also very interested in working to build infrastructure in Africa so that research and research programs can be initiated and run by people who are in

the country who aren't -- who currently don't have the skills necessarily or access to the tools.

And I would close by giving another example like the one that Richard did. It's very clear that genetics -- understanding of genetics of neurological disorders has significantly been enhanced by studies done overseas. I would give you the example of the identification of the expansion of the triplet repeat and the Huntington's disease gene as the cause of Huntington's disease. This was work led by Nancy Wexler at two communities unlike Maracaibo and Venezuela and more recently. And that has led us to understand the pathogenesis of the disease, and also begin to think about genetic counseling and pre-implantation genetic diagnosis. And a second, very recent example is the discovery of the LRRK2 gene, which can cause Parkinson's disease because of its high incidence in Tunisia. So, significant commitment to benefitting treatment of people in developing countries and to building infrastructure and also taking advantage of the genetic discovery opportunities. Thank you very much.

Roger Glass:

Story, that was lovely. A nice review, and I'm glad you don't subscribe to the evil eye hypothesis for seizures.

Story Landis:

Definitely not, but children often are not cared for in the way that they would be if they didn't have epilepsy. So, huge impact --

Roger Glass:

Huge impact.

Story Landis:

-- across the lifespan.

Roger Glass:

Tom Insel, Director of the National Institute of Mental Health.
Tom.

Tom Insel:

Well, thanks Roger. It's unfortunate that Steve Hyman and you have covered much of the ground for why it is so critical that mental disorders be part of a global agenda, whatever that should look like, either at the level of research or policy. I'm not going to add to that except to point out a couple of things that weren't emphasized quite so much earlier in the day.

One being the sense that as we get into chronic, non-communicable disorders, as you mentioned, being the focus for global health in this next decade or so. These are going to be the drivers, and whether they're called neuropsychiatric or how you put them into context, we're talking about disorders of the brain. And there're really two pieces of that that I think Steve emphasized a bit, but probably deserve a little bit of underlining. One is that on the mental disorders side so much of this is in children. These are the chronic disorders of young people worldwide, and that's where the big burden shows up. It's also, though, driven by what Richard mentioned a moment ago: the demographic comparative that at the other end of the life span we're going to see increasing rates of dementia, already more than 50 percent of dementias in the low and middle-income countries. It's predicted to go to over 70 percent by 2030. So, this will really be such a phenomenal imperative for public health needs.

Last thing I'd mention, and Steve sort of hit this but maybe not clearly enough, is if one looks at the millennium development goals related to health, and if you think about the need to have an impact on heart disease and diabetes and cancer and other chronic, non-communicable diseases, you're not going to do that unless you pay attention to the group of disorders that we collectively call "brain disorders." These are, as we often say at NIMH, no health without mental health, and it's just the challenge that we face that we're not going to be able to move the numbers throughout all of healthcare unless we address this group of brain disorders.

It goes without saying, I think, that the disorders that NIMH is most concerned with -- schizophrenia, bipolar disorder, major depression, autism, go down that list -- are not limited to the developed world. The low and middle income countries have essentially an equal and sometime greater prevalence of all of these problems. The value for us in going global is not only that we begin to address this just profound public health need, but we begin to recognize that these problems which exist everywhere are also being addressed everywhere, and there are innovations that we can pick up in low resource environments that can be just as helpful to us in the Bronx or in South LA or in South Chicago as they would be in parts of central Africa or parts of south Asia.

And I'll just give you two quick examples of that. As you look at the way that people deal with serious mental illness, particularly psychotic illnesses, what we call task-shifting and

is a major new strategy in the U.S. for thinking about how to get better care so you can get extenders beyond the limited number of MDs who would be available is done as a matter of course in environments where there's one psychiatrist for 2 million people, which is about the rate you see in lower -- low and middle income countries. A -hundred-and-fifty-fold difference from what we have in this country, but there are pockets in this country where the needs are so great. So, there are innovations that are really critical for us to pick-up on, where we can learn. So, this is very much a two-way street in the global health arena.

There's a second point which is kind of inherent in the way we talk about this. It's really interesting if you look at Steve's slides, he talks about MNS disorders, mental neurological substance abuse disorders. That's a term that's actually come out of the global health agenda, and it speaks to the recognition in the global arena that these are all brain disorders, and that we ought to be addressing them as a single unit, not as eight different institutes that are fragmenting this into different kinds of problems. And in that sense, whether you call that an innovation or just an imperative of the small number of people who can handle this problem, it does point to actually a future that I think we need to think much more carefully about in this country. In a sense, the way in which we're trying to reframe psychiatry as clinical neuroscience is already done every day in low and middle-income countries, where most psychiatrists their number one disorder that they treat is epilepsy. So, it's a really interesting different phenotype that I think we can begin adopt.

This program has been great for us. We have had 29 grants within the Brain Program here. Many of them have focused especially on HIV, and it's both issues related to adherence for treatment, but also behavioral implications. But we're not limited to that. There are some really interesting efforts in Zimbabwe, Nigeria, India, Romania, South Africa, Kenya, Zambia - - really across Africa and into South Asia, and also including Haiti, Egypt, Palestine, that are looking at not only HIV but also some really interesting mental disorders questions.

Just two quick examples. Depression and how it affects learning in Palestinians has been a really interesting project. And a study of how nurses can administer a cognitive test in Zambia to begin to look at the cognitive implications of being HIV-positive. A great example of both the task-shifting idea and

also bringing together the health and mental health issues that we really care about.

So, going forward I think, Roger, there's lots of excitement about doing even more of this going into the future. Probably a shift to bring more of our portfolio here into the mental disorders side or what we'll call the clinical neuroscience side and not exclusively so focused on HIV, but I think those two things can go together, as well.

Roger Glass:
Great.

Tom Insel:
Thank you.

Roger Glass:
Tom, that was lovely. You know, Nora Volkow wrote to me last night and she's at the White House this morning. So Susan Weiss is stepping in for the National Institute for Drug Abuse. Susan, welcome.

Susan Weiss:
Thank you, and actually Nora is not at the White House this morning because she's really sick, and so she had to -- she's been unable to do that as well.

[laughter]

So she -- but she was very sorry that she couldn't be here today. And she asked me to talk to you about three specific areas, two that we're already doing research on in the global arena, and one where we suspect that the United States is going to be a social experiment that might have implications for global health and policy, which is related to our changing policy around marijuana.

So the two of the main areas that NIDA has been supporting research in relate to tobacco abuse, in particular among vulnerable populations including women who are pregnant. We know that the majority of -- 80 percent of the world's approximately 1 billion smokers are in low and middle-income countries, and that's also of course where the majority of diseases related to tobacco addiction are found. And so it's crucial for us to come up with better ways of treating and preventing tobacco use from the start.

Pregnant women is one area that we've had a very high focus on; the other is smoking in adolescence, and that's -- since we know that the adolescent brain is one that is developing and that most people who become addicted to tobacco start when they are adolescents. One of the other ways -- so we are also focusing a lot on treatment for people who are already addicted in terms of both developing new medications, but also trying to expand the delivery of behavioral treatments that we know can be helpful using mobile or e-health approaches that take advantage of social media, phone apps, or other web-based approaches that are widely available in a number of different countries.

The second area that I wanted to touch on is HIV, which Tom has already mentioned. For us, it's a little bit different because what we have been seeing and what we have now had the opportunity to try and change in collaboration with other governments and with other researchers around the world has to do with the treatment of intravenous drug users in order to prevent the spread of HIV infection. And this has been a very difficult situation politically since countries -- many countries deal with it in very different ways. We have -- in this country, we use medication-assisted treatment, and we've found that to be very important in stopping the spread of HIV, but this has been a tough sell for certain countries. And so we have been working a lot in Southeast Asia. We've also been working in Russia to try and convince the government there that the use of medication-assisted treatments for treating particularly heroin addiction or other opiate addiction can actually be extremely beneficial, not just in terms of treating people who are addicted, but also in preventing the spread of HIV.

And we have a number of projects now that are focused on looking at different types of medication-assisted treatment. We now have three main approaches. Two are what people think of as substitution therapies. We don't think of them as substitution therapies, but these are approaches that use methadone and buprenorphine which are agonists or partial agonists at the neural receptor, which is where heroin works. And so, they can be used to keep people from having cravings, but they're also not associated with the same type of rush or other properties of addiction that you see with heroin because of the way -- because of the pharmacokinetics. They are taken orally, and they have long-lasting effects.

The other approach that's now available is something called -- is something which is called a depot formulation, or a very

long-acting formulation of an antagonist, Naltrexone. And this is a medication which was recently approved for treating opiate addiction in this country because of studies that were being done in Russia. And so, Russia has still not -- Russia is still reluctant to use any agonist types of treatment, but they are willing to test this type of approach. So basically our strategy is to try and work in these countries to get them to do better treatment of people who are substance abusers, not only for their benefit but also to help stem the spread of HIV. And we've been having some success, as I said, in both Southeast Asia and Russia.

And the final point that I wanted to come to, which is maybe one of the future directions which does have to do with marijuana policy. As you probably know, there've been -- the policy is shifting very rapidly in this country. We now have two states that have legalized it for recreational use, and we have 20 states that have legalized it for medicinal use, and we're very concerned about the impact that this is having, particularly on young people whose brains are developing and appear to be vulnerable. There's a consensus of data that are accumulating that indicate that people who start using marijuana when they're young and who use it regularly may be at most risk for having changes in their brain development and in fact for having cognitive affects that go along with it. There's one study that many of you may have heard about. It was conducted in New Zealand, and it looked over time at IQ and showed that people who -- looked at people measuring their IQ from the time they were eight and then again at 38 and found that there was a decrease in the IQ of people who were regular marijuana smokers and who had begun when they were young and the decrease was of about eight points, which may not sound like a lot, but if you're at about average IQ and you lose eight points that puts you in the lower third of the population distribution.

Roger Glass:

Susan, let me ask you to pull it together, so we can --

Susan Weiss:

Oh, okay. All right. Okay. When, okay just the last thing then is that we're very concerned about the impact that marijuana is having on youth, and we want to make sure that -- there's a lot of holes still in what we know about it, and so we really want to make an effort to do a large, prospective study involving this country and other countries to try and look at the impact of marijuana on brain development along with other substances.

Roger Glass:

Thank you. Thank you very much, Susan. Bob Kaplan is the Head of the Office of Behavioral and Social Science Research in the director's office. Bob, welcome.

Robert Kaplan:

Thank you. Thank you. It's a pleasure to be here. So, we're not an institute; we are in the Office of the Director with the responsibility of trying to coordinate behavioral and social science research across these 27 institutes and centers. And so, I'd just like to say a little bit about some of the numbers that we have available now, like disability-adjusted life years or quality-adjusted life years, and how that number is driven.

So I think most of us think that if we want to increase the number of quality-adjusted life years or disability-adjusted life years, we do that by investing more in healthcare. But if we look at determinates of health outcome, it turns out that -- and depending on the analysis; there's a lot of debate on this -- but it turns out that most analyses suggest that medical care accounts for only about 10 percent of the variability in what happens to people or what -- how many quality-adjusted life years they live during their lifetimes. And so, perhaps as much as 90 percent of the variability is associated with factors outside the healthcare system. This might include genetic background, but also includes behaviors such as tobacco use, physical activity, social circumstance, and so forth.

So, if you look at the rich countries, like the U.S., we may be investing perhaps 90 percent of our resources chasing perhaps 10 percent of the variability in potential outcome. And so if we really want to determine or we really want to influence this number, I think it's important for us to consider what's happening outside the healthcare system, and we've had a particular interest in this. And I will just give a sort of plug for a meeting that we're sponsoring here in Nature next week that's -- involves what we call the network for inequality complexity and health. It brings together mathematical modelers, epidemiologists, physicians, and behavioral scientists to try to get at this notion of how we model these things.

But if you look at what drives variability, it turns out that healthcare has a bigger impact on infectious diseases, and for non-communicable diseases, it has in many cases a very marginal impact. So the argument is that if we really want to impact

world health, we have to devote more of our attention to the factors that are driving this variability.

So last comment about where we're going in the future. One of the areas that we've been particularly frustrated in for developing these models is the absence of very good data. So even among the rich countries, if you look at a variable like physical activity, it turns out that there aren't good harmonized measures that allow us to make comparisons across countries. And WHO and other organizations have been interesting in this, but over the course of the last 30 years or so, there's been remarkably slow progress. On the other hand, we are hitting an era where there're remarkable new technological developments. So, as populations urbanize, the ability to use sensors or other devices in communities to track people's physical activity and other habits are going to offer all kinds of new possibilities for research. And I think that Fogarty and this community can have a big impact on that.

Roger Glass:

Bob, thanks very much. Gwen Collman represents the National Institute of Environmental Health Sciences and Linda Birnbaum. We heard a lovely presentation about mania cassava toxin. So welcome, Gwen. Tell us.

Gwen Collman:

Thanks very much, and Dr. Birnbaum regrets that she can't be here. She asked me to convey her enthusiasm for global environmental health issues and for our long-term partnership with the Fogarty International Center.

So, NIEHS's mission is to discover how the environment effects people all around the world in order to promote healthier lives, and our institute does that by conducting research on environmental chemicals and other environmental exposures on many organ systems hoping to discover the mechanisms of action of these exposures and to discover the risk of disease in many vulnerable populations. We're dedicated to reducing exposures, and we do this in a preventive framework knowing that it is better to prevent disease than to cure it later.

Recent scientific advances encourage a life-course approach to environmental health research, and we heard a little bit about that in our earlier panel today. We know that exposures during specific developmental windows, specific times across the lifespan can lead to different risks of disease, and this is particularly true on the brain. We have a lot of data amassed

over the years on a variety of environmental chemicals that affect -- that can be documented either during gestation or early life that effects the nerve development of the growing child. And exposures early in life and also later in life can affect cognition and motor function in adulthood, and we have very strong portfolios in each of these areas.

Often research in different parts of the world have led us to preventive strategies here at home. Some of our best examples are exposures to lead, mercury, and arsenic around the globe, and we've learned a lot about how exposures to these metals have affected the brain of growing children. And we see evidence from Australia and Yugoslavia for lead which points to deficits in IQ; and for mercury in the Faroe Islands in the Seychelles studies also combined with exposures to chemicals like PCBs that have also affected intellectual function. Arsenic in Bangladesh and Chile were thought to be cancer-producing, but of late we know that early life exposures to arsenic can also be developmental toxicants for children.

And our involvement over the last decade in the brain disorders program with the Fogarty International Center has led to the funding of about 20 grants. And now as we support research on a wider variety of exposures, and these exposures are of local concern to these countries. So, pesticides of a variety of kind, industrial pollution, variety of metals, outdoor air pollution, and indoor air pollution from cook stoves affect the populations in countries in Asia, Caribbean, and Africa.

And when I talk about local concerns, I particularly think that's important, because we know that -- we know the health effects of many of these exposures from studies in other regions. But at -- for local public action and public health practice, data really needs to be developed locally with the appropriate cultural sensitivities, in order for public health action to be put in place.

So, over the last 15 years, we've partnered with the Fogarty Center and the National Institute of Occupational Health and Safety on the International Research for Environment and Occupational Health program, ITREOH, and now that program has phased into a new program called GEOhealth. And these programs combined with the brain disorder program really leverage resources across many different areas for training of NPH, PhD, medical students, physicians, and other scientists to participate in important environmental health research within their own countries, to have training opportunities here within

the U.S., and then back at home, building talent capacity, local infrastructure, and collaborations around those local environmental health problems, and they do lead to important public health outcomes.

So as NIEH has moved forward, global environmental health continues to be and maybe even more so a strategic priority found in our strategic plan, and we're elevating our investment in these areas. We've just been designated a WHO collaborating center on environmental health, and in this regard, we're working to build and coordinate a global network of children's environmental health researchers and working to assist WHO to translate the research on environmental exposures in early life on diseases, such as intellectual disabilities, growth and development, ADHD, respiratory disease, and obesity. Working with the WHO will bring together scientists and policy makers of environmental ministries to discuss exposure cleanup and reduction and possible public health impacts and to promote disease prevention through raising awareness of the environmental risks associated with high levels of these pollutants in the developing world.

Thank you for highlighting some of our work here at the symposium today and also congratulations on the 10 years of this outstanding program, and for Fogarty's leadership in this area.

Roger Glass:

Okay. Thank you very much, Gwen, for that last plug in particular.

[laughter]

Ken? Ken, you're dealing with a toxicant that many of us have experience in. Ken is the director of the National Institute of Alcohol Abuse and Alcoholism. Tell us how you see this program

--

Ken Warren:

Okay.

Roger Glass:

--in the future.

Ken Warren:

Okay. First I want to acknowledge that I'm currently the Deputy Director, again, of NIAAAA, and, but I did serve a role as the Director, and worked very closely with Fogarty in that, during

that period. And again we have certainly enjoyed our collaborations with the Fogarty Centers.

What I'd like to start off by saying is that alcoholism itself or alcohol dependence itself is a brain disorder, but a major part of our international program has focused on alcohol as a toxicant or as a teratogen which is capable of causing significant birth defects including those that affect neurodevelopmental behavior. The fact that alcohol is a teratogen was not recognized in the United States until the -- very, very surprisingly until the 1970s. And around the world, it has taken even longer for this recognition to come about, and this is one of the reasons or some of the efforts that we have been involved with in trying to change that perspective and to increase knowledge and basically to try to uncover the scale of the disability around the world. I wanted to start with a new program which has been underway only for a few years in fact it's in its early stages, and this is a collaboration that we entered into with the World Health Organization.

Now another very, I think not too surprising and not too shocking statement is that -- as though since we know the ideological agent involved in what is called fetal alcohol syndrome or fetal alcohol spectrum disorders. Since we know the ideological agent in its alcohol, in those countries in which the alcohol consumption is greater and especially where alcohol consumption is greater in the pregnant women population. These are the countries where we expect to have the highest prevalence of FAS. And so far, every indication is that that indeed is the case. The World Health Organization became very concerned about two parts of the world sub-Saharan Africa and Eastern Europe, and we have worked with them in basically developing a program that involves training in the -- with research personnel in the recognition of FAS. And so that prevalence studies can be undertaken in these countries. We've had two major trainings joined with the World Health Organization. Approximately three years ago, we had a training in Eastern Europe with Belarus, Ukraine, Kazakhstan, and Moldova. Moldova, by the way, according to the WHO statistics is the country that has the highest prevalence in Europe of alcohol dependence among pregnant women, so it's the country in which would expect to be a high risk there.

And in Africa, just last year, we had a training with Kenya, Tanzania, the Seychelles, Ghana, Namibia, and Ethiopia, and projects are currently getting underway -- projects are well underway in Poland. Now Poland has joined the group even though

it is a high-income country, so it is not specifically sponsored by WHO because WHO is only sponsoring countries at the low-income or middle-income level.

So the -- again by increasing the knowledge of the extent of these disorders of the population is the intent to basically increase the focus, increase the knowledge in terms of the extent of the disability and the importance of this disorder as a public health problem. It is -- I emphasize the public health problem aspect of it because in every place where we've looked where we see fetal alcohol spectrum disorders, it is a major problem or it is one of the major problems, if not the major problem, of neurodevelopmental disability in children. I just want to highlight, also that our work around the world actually began in the fetal alcohol syndrome area. First in South Africa when we started to work there in 1996 and that both -- the countries we have worked with including South Africa as well as the U.S., we have both benefitted by this.

South Africa gave us the opportunity to have access to the types of populations we could not study in the United States because most children in the United States with fetal alcohol syndrome were put into foster care and are therefore not available to the researchers. In South Africa, this was not the case, and plus by an unfortuitous act [inaudible] of history they have a population there that historically drinks at very high level, so they had very high prevalence levels -- prevalence levels 10 times higher than in the United States. Well, we have many projects going there, and we have many projects going in other countries including using nutritional fortifications for example of folate and other vitamins to try to offset the problems of pregnancy going on in such countries as the Ukraine. And of course we have our research joint with Fogarty in Russia that will be presented in more detail tomorrow. Thank you.

Roger Glass:

So you've heard now really extraordinary partnership at NIH from nine leaders. A third of the leadership of NIH is on this stand right now, which is extraordinary. This program would not have happened without their full participation, so I think they all need a round of applause, just to recognize that.

[applause]

And I have to add that they all contribute to our Fogarty Fellows and Scholars program, so that to the extent to which we send young American investigators and support foreign

investigators that partner in these programs, this is our -- another way that Fogarty can contribute to building up the network of research that exists.

Now I want to give -- we have about 20 minutes left. I want to give you -- some of the people in the audience a chance to ask questions. While you're honing your questions, let me throw out to the group, where do you think we should go from here? We've been in this program for 10 years. I think it's grown up from a crazy idea of what's in it and what will we get out of it to an incredible success. And as you can see from the contributions of research, the partnerships, the peer review grants that are involved, what's the next step as we move forward?

Who can I call on first? Tom, you're looking at me.

Tom Insel:
I've learn not to do that again.

[laughter]

A thing we call single-trial learning, Roger. Let me just throughout a couple of ideas that you just already heard that maybe to summarize comments from my colleagues. I think first the idea that there will be population islets that provide a particular opportunity of great interest, and the ability to do that and to do it well, whether it's alcohol or a rare mutation for dementia or for Huntington's disease, that continues to be a place where we should all think about learning something special.

Second, that Susan and others mentioned was the chance to think about how technology will really change the landscape for all of us. It's an opportunity, it's also a challenge in different ways. Current estimate is that there are 2 billion cell phones in use. The estimate is will be that number will go to 6 billion by the end of this decade, or within something like three to four years. So, it's going up very, very quickly. What that means for how we deliver care of the kinds of sensors as you were mentioning that one could build in to collect data. I mean, it's a real gamechanger, and I think thereto the global perspective is going to be critical.

Third thing I'd mention I think is just -- and we didn't say this explicitly, but it needs to be said at some point today. That when we talk about global, it's not the same as talking about international or foreign. That global is -- I mean we're

all in it. And that those issues that we're addressing, whether it's through this Brain Program or other programs that Fogarty develops, they're important for everybody everywhere, and that's the way we should define them, and I think we need to communicate them that way.

Roger Glass:
Alan.

Alan Guttmacher:

I just want to develop a theme that Tom has brought up in two different ways, both in his comments and answer that is the benefits of global health research to those of us in the U.S. and clearly in pediatrics. I know I told Roger about this because he was very much involved in it. We have examples of, in fact, not just the benefits of that accruing to the Bronx but to Westchester in for instance for rehydration therapy. The ability in other circumstances to think more innovatively about the questions and to come up with models for dealing with them that for various reasons having to do with our healthcare structure are the kinds of things in the U.S. we're less able to have these original ideas sometimes.

Another resource, poorer conditions to come up with much more innovative thinking I think is yet another advantage of us doing this. And as we move forward, it's hard to think ahead of time about those things you haven't thought about, but as we design forward steps, we need to keep trying to take advantage of those kinds of opportunities to really innovate in a way for various reasons we cannot do so well here.

Roger Glass:

Okay. And -- hold your questions and come to the -- go to the microphones. When I start seeing people at the mic I'll continue, but I would say one other issue that you've raised with, not only new technology, but we really actually have new platforms in the developing world. I look at Tom and I think about your Centers of Excellence in three areas. I think about the impact that AIDS has made around Africa to provide a research infrastructure upon which we can think about ethics and informatics and research administration. I think of the MEPI program that we have at Fogarty supporting centers in Africa in twelve countries. I think of the H3 Africa of Dr. Collins and the genome which has given genomics a voice and a research base so as we begin to think about unusual populations with neurologic diseases or genetic disabilities that relate to the brain -- there's an opening there, as well as the Centers of

Excellence that you mentioned. So there's new platforms to work with in the new developing world.

Neither of you have said anything about the Brain Initiative, which is global and which is big and which is in the paper story. Do you want to say something?

Story Landis:

So, this is the Brain Initiative, brain research through advancing innovative neurotechnologies which was announced by President Obama on April 2, 2014, and now has a preliminary plan that has been accepted by the Advisory Committee of the Director of NIH and RFAs are out. This is meant to create tools that will allow us to study the brain in real time with the resolution that we've not been able to do before. What's particularly interesting about this is that we weren't the only country to discover that the brain is incredibly interesting, exciting, and important, so there is a brain project in the European Union which is very different, but extremely complementary to what we're doing and other countries are beginning to follow suit. I think that the kinds of tools that will come out of this and insights that will develop about how the brain works will be significant for understanding MNNS disorders, not only in developed, but in developing and low and middle-income countries, so we're incredibly excited about that, and very interested to see what the additional brain projects will occur in countries that have not yet announced their intentions.

Roger Glass:

Great story. Well, with that, we have a whole bunch of questions. Let's make your questions short and to the point, and we'll try to get some rapid answers so everyone has a chance. Start right here.

Male Speaker:

[unintelligible] University of Pittsburgh. I just want to know if Fogarty is planning to partner with LMIC countries for funding research proposals. I think NIH had a couple of initiatives last year where they jointly funded research projects in India and China. Are there similar plans in progress?

Roger Glass:

Yes, we're working with South Africa. We will be in discussions with Brazil; we're talking with Mexico. So we would love to see these opportunities emerge because as we said, these are global

problems. They're not just our problems, but they're problems that we all share, and I think the solutions will be solutions that we will all like to participate in. Next, on your side.

Emmanuel Peppron:

Yes, this question is for -- excuse me.

Roger Glass:

Introduce yourself, please.

Emmanuel Peppron:

Oh, Emmanuel Peppron [phonetically spelled] -- Dr. Landis. Dr. Landis, you alluded to NINDS's interest and capacity building in Africa. Could you elaborate a little bit more on the institute's vision? Thank you.

Story Landis:

So I think what -- the vision's not very visionary yet. It's that just as there are very few psychiatrists in developing countries, there are very few neurologists and that we all know that many of the neurologists who are trained and are coming to the States because of the opportunities for research, and so we have partnered through MEPI and H3 Africa to fund projects that are building that kind of capacity, and we also have a program that is collaborative with the intramural neurogenetics program that Kurt Fischbeck runs, which is working on helping in working in Mali think about genetic disorders that affect the nervous system and how in a developing country you might approach not only gene discovery, but counseling and incorporating the recognition of the genetics in causing disease.

I think we struggle with if you're going to invest, how much do you put into research projects which can actually be transformative as the examples that I gave you have been. Neurocysticercosis in Peru will now be treated very differently than it would have been if it weren't for the trial that we've done, Ben is making a huge difference in Uganda, and I think the epilepsy project. And so what the right balance is between infrastructure and specific projects that could be transformative is something that we struggle with every day.

Roger Glass:

Next question. George?

George Hill:

My name is George Hill from Vanderbilt University's School of Medicine in Nashville. I serve also on the Fogarty Scientific

Advisory Board, and in that capacity, I really want to thank you all for your participation, funding support, and just being here as well as supporting Fogarty because we know without your type of support, it would not be there.

And so my question goes to what Roger raised at the beginning, and that was what do you see in the future? And it dovetails on the comment that was just made -- the question that was just asked, and that is if you look in your crystal ball, do you see some new type of programs that might be helpful when it comes to increasing training of individuals in developing countries. If you could fund with limited money a particular approach, what might it be? And again, thank you very much for your support.

Roger Glass:

Who wants to take that last one?

Tom Insel:

I think I'll say something about that. Thanks for the question. What we decided for NIMH was that the need was urgent enough that we would do this independently of Fogarty. So as Roger mentioned, we established these -- essentially they're footholds, they're Centers of Excellence in -- one in South America, which we haven't talked much about so far today, one in Southern Africa, and one in South India -- or South Asia, too, that would become the place for training and provide enough infrastructure that people could begin to get going in this case with a focus on serious mental illness, especially psychotic illnesses, and actually beginning to run both biomarker studies and trials in that environment. It was -- it's been a bit of a saga; it has not been easy, but I do think that once you have that foothold, there's an opportunity to support the training, and that's where we would really love to work with Fogarty to build that out. And you've got a place for people to work, and you've got the structure there for them to be productive.

Roger Glass:

And I think these things take a while to mature. You don't get a training and a research center up overnight. Let's have another one here, and then we'll go back to the other side.

David Warburton:

Thank you. I'm David Warburton. I'm from the Children's Hospital in Los Angeles and University of Southern California, and I'm wearing my Fogarty hat today as you can see. I have a D43 in Mongolia which is dealing with pollution; it's funded by NIHS, thank you very much. We're also interested in the Congo.

So when you sit down with senior government in these emerging countries -- presidents, prime ministers, and ministers -- they really want to know two things: number one, if you're making a recommendation about some intervention be it mental health or pollution, whatever it is they want to know is this going to be popular, and if it's going to help me get re-elected. They want to know that, and this is no joke. This is really important. And secondly, they want to know if I spend part of my \$50.00 health budget on this, will I have money left over to allocate something else, or better yet, will it be a multiplier effect in the economy which can be calculated in the millions or billions of dollars and will that occur within three years, five years, seven years? And this absolutely critical in terms of getting your killer app intervention done.

In Mongolia, for example, if we could get rid of coal burning for domesticating -- bingo, we wouldn't have any pollution. You think that would be a no-brainer for the government, but they ask you these two questions. Would it be popular, and what would be the multiplier effect in the economy because we would have to spend \$600 million to do that. So that's my comment, and I just want to know if anyone on the panel thinks that econometrics and political engagement is something we should be thinking about as opposed to pure research if we actually want to get this done.

Roger Glass:

Policy. Tom, go ahead jump in.

Tom Insel:

So, let me jump in. And these are great points. I was at a meeting with health ministers from the developing world about two weeks ago and giving a presentation very much like what you heard from Steve Hyman, and the Health Minister of Pakistan got up and said, oh this great, but you have to understand brain disorders or not part of the MDGs. If you're not on that list, we're not going to pay any attention, it's that simple. It's not that we like that, but that is how we are judged. It's just like being an elementary school teacher where you have a checklist of things you have to do within the year. This isn't on our checklist, and it's not going to get done. We don't have the resources to even do the 15 things that are on the checklist. Don't give us a number 16; it's not going to happen. So it does speak to the importance for those policy folks to actually have some representation from the UN MGDs, and if this

is getting revisited in 2015, I think it requires some input from all of us to make sure it's a priority.

Roger Glass:
Gwen and then Alan.

Gwen Collman:
I was just going to briefly say that at NIEHS, we often and encourage these environmental health studies to be done with community engagement and involvement. So questions about will they like it and will these interventions or the research be popular can be discussed up front and the research can be designed in ways where you can translate the results of it more quickly because you're working with the right people in the communities.

Roger Glass:
Alan?

Alan Guttmacher:
I do think that we have both an opportunity and a necessity to do the kind of econometric research to really inform policy. We for instance at NICHD have long supported the Nobel Prize winner work of Jim Heckman showing their early childhood intervention in the States actually does pay dividends financially. That needs to be done more on a global sense. Now, of course, it gets more complicated because if you're really going to do the rigorous kind of econometric analysis it's not universal. The impacts of those vary by culture, by nationality, by economic systems, et cetera. But those kinds of -- to some degree approving of what we assumed to be the case, but it's not always the case. So I think that kind of thing is very important that we fund.

Roger Glass:
Great. Narendra? [phonetically spelled].

Narendra Arora:
Thank you very much. I'm Narendra Arora from INCLIN in Delhi.

Roger Glass:
They don't know what INCLIN is, better to --

Narendra Arora:
The International Clinic Epidemiology Network. We are based in Delhi now, but present in other lower and middle-income countries. Thank you very much for exposure to such a

distinguished panel. I want to make a couple of points, and that relates to if we talk about diarrhea, poverty, drug or substance abuse, environmental issues, we find the drivers of most of the mental disorders or brain disorders reside outside the health system.

The other issue is of the resilience, brain resilience and the rapid transition which is occurring in lower and middle-income countries particularly. And so I -- my suggestion is and I would request the panel to respond to that that is there a program of linking brain to society? It is very important to double up coalitions between various sectors, and this is a difficulty, sure, and requires a generation of evidence.

Roger Glass:

Linking brain and society. Bob, is that in your domain?

Robert Kaplan:

Maybe. Well, I think it is important again when you look at the determinants of health. So what factors are associated with production of disability, adjusted life years? So then most of them do reside outside of the healthcare system, and that, you know, we know even begin in rich countries that the very best predictor of longevity is educational attainment. So I think that this is an important area, and I want to commend Roger because we at the NIH don't do a lot of population health, and I think that Fogarty is the one focal point within the National Institutes of Health that takes a population perspective.

Roger Glass:

I would say aging also because the aging surveys that are done by the National Institute of Aging have been extraordinary for their global perspective and economic inputs.

Richard Hodes:

Just to comment further, this comes from overlays of a lot of what's happening. The challenges are huge as we've heard, but maybe what has been underemphasized is the challenge that comes with the incredible pace of change in environments in much of the world, in particularly the developing world. The accommodation that the healthcare system that research has made to conditions of older age to changes in the balance of acute infectious versus chronic disease has had the luxury, if you will, of happening over decades, even centuries.

The pace of those same changes is in the developing world is huge now, so when one sits down and talks about policy and

ministers and what's important and what's on the list, as difficult as these are to be foreseeing, predicting what's going to be the balance of priorities in years to come is huge. So it's all the more imperative for us to establish means of surveillance and communication that allows and informs policy makers as well as the implementers to not only address what is happening now, but to project into the very rapidly changing prospects for the years to come.

Roger Glass:

Adnan? We'll take just take about two more questions and that'll be it. Adnan?

Adnan Hyder:

Thank you very much. Adnan Hyder, Johns Hopkins University, Bloomberg School of Public Health. Thank you very much, first of all, for the support that all the institutes give to the various grant mechanisms.

I wanted to basically raise a challenge to you all. Earlier this morning we heard from Dr. Hyman how he was puzzled despite the burden numbers of neural and mental health disorders, policy makers are not paying attention. I'm concerned about your attention to a field of injury and trauma research. It's very clear that the numbers are extreme. The global burden of disease and any other numbers you pick up talk about this extremely large burden of injury and trauma around particularly in developing countries. It's also reasonably clear from the literature that they act as causes as well as consequences of neurological disorders, of mental health disorders, of brain disorders, but some of us are quite puzzled as to why your institutes may not be paying enough attention on those. So I'd like to challenge you to see -- are you listening to the evidence? Are you also like policy makers blind to some parts of the evidence? Thank you.

Roger Glass:

Story? I --

Story Landis:

So I think that trauma, particularly brain trauma is -- we're the league institute for that, and we have funded projects through this program in South America, and I think we have one or two others that are addressing some of the common causes. As people get automobiles and bicycles and become more mobile and live in cities, there will be more of that. There's the public

health piece I think that you're alluding to which is prevention, and we are concerned about that.

I would say in terms of treatment and rehabilitation, we have not until relatively recently been as focused on that because there really didn't seem to be opportunities. We have people on my staff who have argued for decades. A decade and a half that it's one of the highest burdens and it's where NIMDS has invested the least money. There's something like 30 clinical trials dealing with brain trauma which have failed to provide any compelling data on treatment, and we share rehab with NICHD and there's not the level of evidence that we'd like there either.

We have two studies underway, one in collaboration with Europe where we will be looking -- we each will be looking at 5,000 TBI patients, different kinds of TBI and each of them will be treated as the Center feels is best practice and then we're going to try and extract from that soup what principles we might and then test them in real randomized blinded trials. And we also have a project in the states looking at TBI in children and here with several hypotheses that will be tested as a 1,000 children are tracked.

But I think we can have the biggest impact through programs that work on prevention. Bicycle helmets in this country has made a huge difference. I don't think I've ever seen a picture from a developing or low or medium-income country of a person on a bicycle with a helmet.

Roger Glass:
Alan?

Alan Guttmacher:
I'm going to disagree and then agree with the base [inaudible] of your question and that is I think that -- I know we've long been quite interested in issues of trauma and funded a lot of research in that area.

On the other hand, I think you're right that we haven't given as much attention as it's due. NICHD recently went through a reorganization of our structure, et cetera in that we created two new branches in our extramural program, one of them specifically name Pediatric Trauma and Critical Illness because we thought that our long-time interest in trauma needed to be better advertised, and we also need to be more creative in funding opportunities, et cetera. I know that Valerie Maholmes

who is the branch chief of that new branch is someplace in the audience; I saw her earlier. So if any of you have thoughts about interesting research that we should be involved in trauma that we're not already involved in, we'd love to hear about it.

Roger Glass:

Let me ask the three of you standing to give your questions quickly, 30 seconds, and then we'll have the panel give a last sum up.

Leslie Davidson:

Leslie Davidson, Columbia University in New York. My question really was the utility of using the convention on the rights of persons with disabilities, which has been signed onto by almost every country in the world, barring the U.S., which never signs any convention, but it would seem to me it both brings potential partnership with countries and translation of findings into action in countries, and is therefore a hugely important tool. Have you thought about it?

Roger Glass:

Next question.

Female Speaker:

Actually, two brief comments. First of all, [unintelligible], Yale University, and our project is not funded by any of you, but it's funded by the Fogarty directly, and I just really would like to acknowledge the institute in this role as a funder, and Kathy in particular is the program officer and the inspiration of this program. Just thank you from all of us, I suppose.

And also the question is, what I was struck by listening to all of you is how much emphasis you have given to IQ, and as a -- you know, I think five of us go into it as an outcome, but what about positive outcomes? And what about achievement, academic achievement, what about success, what about happiness?

Roger Glass:

Okay.

Female Speaker:

Any thoughts about that?

Roger Glass:

Okay. Happiness and positive outcomes, and Gretchen, it's the last question.

Gretchen Birbeck:

And I'm going to end on a negative note, sorry. We are all preaching to the choir here when we talk about the importance of global health, but you guys have to speak to a much broader audience at a time when funding lines are grimmer than ever. So what can you tell us about being better marketers for you? Because all of us in this room, we all agree, but if there's a much broader constituency that needs to be addressed.

Roger Glass:

So marketing, positive outcomes, who wants to take a pitch on the -- well, maybe we'll go down and just let you each say a final closing comment.

Alan Guttmacher:

I think that's actually a nice lead in to what I would say is the closing comments, and that is that too often, I think particularly for people who are not directly involved in it, the idea of U.S. involvement in global health is this kind of lady bountiful model, that we will go take our largesse to the developing world and do that kind of thing. Now that may not be a bad thing to do, but that's not actually most of the reason for doing it.

So talking about the bi-directionality, the really arboreal nature -- it's even more than bidirectional -- of international health and being able to talk with people about how global investments -- because some people are very shortsighted in where they -- how they want to see their investments pay off -- but talk about how that really enriches the U.S. in various kinds of ways is something that we don't do a good enough job. Now it's not an elevator speech, it's a conversation, but in developing that more is something that -- because we are the experts, we know about that, but we don't talk about that enough.

Roger Glass:

Richard?

Richard Hodes:

Yeah, I couldn't agree more with what Alan has just said. There are multiple rationales, justifications, all of which have to be invoked. There are always going to be those who find the highest priority to be the self-interest of this country, and there's nothing wrong with that if one translates it into a broader understanding of the way in which we are citizens of the world. Very few of the problems that we have are not shared.

The opportunities to inform to the benefit of this country are usually overlapping with those of the globe.

I would say in terms of needs to come, let me just finally indicate that it's been noted, the need for more infrastructure, which will be facilitated I think by technologies. Not so long ago we found it hard to imagine even developing the database to understand what the problems were globally, much less intervene in clinical studies and trials. The use of electronic monitoring is an opportunity we need to take maximal advantage of, and I think the growing number of global health meetings we have, which are bringing together not just the scientists, who have no trouble with agreement, but the ministerial level of policy makers, which vary in identity from nation to nation, is a positive trend, I think, that we're pursuing hopefully with a productive outcome.

Roger Glass:

Thank you, Richard. Story?

Story Landis:

So I would just say, I don't think that -- at least I shouldn't speak for all of my colleagues, but I don't think that my institute does nearly a good enough job of making the case for the benefits of our budget. It's an investment, not an entitlement, and discovery leads to significant benefits for health and for the economy. I'm not sure that one would want to single out global health as making the argument for the NIH budget. I think we need to make the argument for the NIH budget, and -- in general and that global health needs to be a piece of that. I know most institutes don't not fund grants in global health because they think that Congress will look askance.

Roger Glass:

Tom?

Tom Insel:

So I agree with everything you just heard from my three colleagues. Let me go to the second question, which was about IQ or finding happiness as a potential outcome. And because we are the National Institute of Mental Health, often that question does get posed to me, what do we do in the realm of happiness, and I would say we do as little as possible.

Our institute is very focused on deadly diseases that we're trying to save lives for, and that these are really serious,

most disabling illnesses that we can think of and that we know about globally, and so we've got a big challenge in front of us, to save lives and to reduce disability. So we are focused on that.

But I should amend that to clarify that we're not in the business of defining success by reducing symptoms. Our definition of success is improving function, and that means getting people back to work, getting kids to finish their education, getting patients to define what it is that they want, and helping them to get to that. Happiness is usually not exactly part of the equation, but maybe when we solve all the other problems then the NIMH can actually become the National Institute of Mental Happiness.

[laughter]

I don't see that happening in my lifetime.

Roger Glass:

Isn't there a happiness ratio for countries?

Tom Insel:

There is, but actually we're -- you know, I think we need to be really careful about that. I think we want to focus -- I mean, in a way that trivializes the problems we're dealing with --

Roger Glass:

Yeah, yeah.

Tom Insel:

-- and I don't think we want to go down the wellness-happiness line.

Roger Glass:

Susan?

Female Speaker:

Yeah, we also get asked a lot about happiness and why we don't look at some of the more beneficial effects of drugs, but that is not our mission either.

[laughter]

So I would also -- I would like to concur with my colleagues as well in terms of both the importance of the bi-directionality. For us, I think it's really important that we also -- we also

keep the public health and the policy focus, because a lot of the areas that we're interested in are very highly stigmatized, and they're being treated very differently in different countries, and we hope that we can improve the public health overall.

Roger Glass:
Bob?

Robert Kaplan:
Well I -- maybe I'll return to what I said at the beginning, which is I continue to be frustrated about quality of data and harmonization across countries, and I do think that we need to pull together to find ways using new electronic technologies and other methodologies to come to a better understanding of these problems. Actually, I was interested in the comment from the gentlemen from LA Children's, because Los Angeles County Public Health Department does an unusually good job in doing health impact assessments; so looking at all policies in terms of how they will affect the health of the public. And I think that those models are evolving; they're not quite there yet, but have the potential to make a big impact in the future.

Roger Glass:
Gwen?

Gwen Collman:
I think I'll close by speaking to the investments issues. So as each of the institutes have invested in infrastructure and population studies around the world, I think we all need to be open to studying other endpoints of interest across the NIH, and across the needs of the global societies. Times are tighter, so I think we can make more of our investments by adding different exposure scenarios, different windows, and different endpoints, and we can use the expertise of our collective grantee communities to help us with those tools and measurements.

Roger Glass:
Great. And last?

Ken Warren:
Okay. Last of course is the last person down at the end here. I'm going to have very little to add, but I'll just go ahead and focus on two aspects, too, and the first of which is, you know, a thing which I did, which I spoke on, and I think others spoke on as well, is the fact that global health research really benefits us, and that's why it's worth the investment, and it

certainly in the case of the disorders that we study in our institute, we couldn't do it -- we couldn't do it well without having the global health approach, because it's -- it makes it more complicated to try to do it solely within the United States. And the -- I think I'll just end it at that point, and given that it's been a long day -- a long session.

[laughter]

Thank you.

Roger Glass:

Let me thank you all for being up here. I think it's been a wonderful session. We've covered a lot of areas. I know Dr. Collins wanted to be here, but was unable to be here to join us as well, because this is a commitment for him as well. I don't think your -- it may take us a few years before we get all of these NIH directors and leaders on the panel talking about global health again, so I really want to thank them all. I'm a little bit like the concert master; I don't play an instrument, but I can try to make the violins and the clarinets and the trombones all play, and I think they've been absolutely extraordinary. This program would not happen without all of them. Thank you.

[applause]

And just to warn you, there are posters upstairs, there are a lot of posters that are wonderful and will let you interact with people. You have to be back here at 1:45 for the plenary and lunch is over in the -- right next door, in Natcher. Kathy, thank you.

Kathleen Michels:

Thank you, and thank you for a wonderful panel. In addition to the lunches -- in addition to the cafeteria and the snack bar, a number of you pre-ordered lunch, which is a really good idea, because you see there's a lot of people. Those are out on the registration desk. So yes, please be back by 1:45, and those of you who have a -- the session right after 1:45, if you can be up here and on the panel ready to go at 1:45, because we will start at 1:45.

[break]

VI. Plenary: Burden of Nervous System Disease and Disability in the Developing World

Kathleen Michels:

-- the afternoon session will be starting now, and Dr. Kaplan will be the moderator, and so without further ado.

Robert Kaplan:

Thank you so much. I'm going to do a very brief introduction to this session, but also explain why I think this is such a particularly important problem. So I'm Bob Kaplan. I am the NIH associate director for the behavioral and social sciences, and I am -- became very interested in these metrics to quantify the impact of various factors on health outcome some time ago. This is very much relevant to the NIH mission statement.

So here at the NIH our mission is science in pursuit of fundamental knowledge about the nature and behavior of living systems, and I think this is what most people recognize as what the NIH does. But there's a second clause to our mission statement, and that is the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. And I've been particularly interested in, well, how is it that you quantify whether or not we're making progress toward this goal.

Traditionally we think about measuring health outcome using these basic measures: life expectancy, infant mortality, and disability days. But unfortunately, these have limitations. So life expectancy, for example, is a great measure, but it doesn't take into consideration what happens to us during the portion of our lives that we're alive. So we experience different levels of illness and disability during that period. Infant mortality, of course, a great indicator for global health studies, but doesn't take into consideration what happens to people after that first year of life. And disability days, which is a good metric, but no one's ever been able to figure out how to use it in policy studies.

So about 40 years ago, I joined a group at the University of California in San Diego with the goal of developing some sort of metric to measure the health of nations, or the health of any sort of program. We realized at the time that survival analysis, although it was a great metric, had one basic flaw: that you were scored as alive if you had -- I mean, you scored as 1.0 if you were alive, and you were scored as zero if you're dead. It didn't take into consideration what happened in between.

So for example, this person out playing tennis is scored as 1.0, but a person in a coma is scored as 1.0 also. And so we thought that survival analysis was a great idea, you got a point of credit essentially for each year that you complete, but we needed to refine it so we can take into consideration these variables that make the tennis player be scored differently than a person in a coma.

And so the goal of these metrics is to summarize the life expectancy with adjustments for quality of life, and I won't go into the details of how we do this, because it takes too long, but roughly you might take a person who in this case lives about seven years, and for the first year -- or first two years of their life, they're scored as 1.0, they are in almost perfect health, and then the next year and half, it's weighted as 0.7, because they're about seven-tenths of the distance between perfect health and death, and then they get quite sick for about a year, scored as 0.3, and then they come back for several years at a health state that's weighted about 0.9. So if you sum this up, the seven years that this person lived counts as about point -- 5.6 quality-adjusted life years, or they lost about 1.4 equivalents of life years because of illness and disability.

Well, some years later, the Global Burden of Disease Group and the World Bank developed metrics somewhat like this. It was actually about 15 to 20 years after we had first got started on these metrics. It was realized that there was just too much emphasis in our usual metrics on infectious disease, and that at the time it was felt that mental illness may be the number one threat to worldwide health, and that non-communicable problems, like smoking and traffic accidents were probably second and third.

And as Dean Jameson pointed out at the time, way back in the beginning of this exercise, that if you don't use some sort of disability weighting, then you come to wrong conclusions. So for example, psychiatric illness, he thought at the time was going to account for much more of the total burden of disease, just as deaths associated with road traffic accidents. So I think I'll just skip this because it's too complicated, but I just want to kick this off today by saying that, if we look at the most recent publications from the Global Burden of Disease Group, you'll see that across different regions of the world, the red areas -- in this case, these are mental and behavioral disorders -- and then the one below it -- let's see if I have the pointer, oh -- the orange-est color below that are neurological conditions in all regions of the world account for a very

substantial portion of the total burden of disease. So if we look at our traditional metrics of infant mortality, life expectancy, and so forth, we might completely miss this.

So today we'd like to address problems relevant to this, and I'm going to introduce the three speakers very briefly. It's a very distinguished group, and you have bios in your packet, and I was asked actually, because of -- in the interest of time, we need to keep moving -- I'm just going to say a few words about them. But actually it's a pleasure to be part of this group.

The first keynote speaker is Donald Silberberg. Dr. Silberberg is professor emeritus at the University of Pennsylvania. Actually he's been at the University of Pennsylvania since 1963, so he has had a long run there. But I want to say that before that he actually trained here at the NIH, so I want to welcome him back to the NIH. Dr. Silberberg has had a very profound effect on this field.

So some years ago, he helped organize the Institute of Medicine study on the talk that we're going to discuss today, a neurological illness and its effects on global burden, and that he was quite influential in not only putting the study together, but helping raise the money for it. He also, as I understand, was able to engage Kathy Michels quite early on, and so that they've had a long-standing relationship in pushing this agenda forward. So welcome, we'll hear from you in just a minute.

Now the second speaker is Narendra Arora, who is currently with the INCLLEN program, funded by the Rockefeller Foundation. Dr. Arora's trained at the All India Institute of Medical Sciences University in New Delhi. He had a brief stint where he went to Australia and was at the University of Newcastle, which is, you know, as I think many of you know, an international leader in biostatistics and epidemiology, and he's come back to lead the INCLLEN program. So, welcome.

And finally we have Dr. Leslie Davidson, who is appointed jointly at -- by the School of Medicine and the School of Public Health at Columbia. So she is a pediatrician, epidemiologist, and she is the leader of the epidemiology PhD. program at Columbia. So, welcome. And with that, I think I'll get out of the way and introduce Dr. Silberberg. So welcome to all of you.

Keynote: History and Context, the Burden of Neurodevelopmental Disabilities

Donald Silberberg:

Thank you very much, Dr. Kaplan. And let me just say that it's an absolute delight to see what this program has become. And I'll just say again, I think it was mentioned earlier, and it's obvious to a lot of you who know her and know the program, that Kathy Michels has been the spearhead in making this all happen over the past decade -- or actually, a little bit more than a decade. I'd like to get to my slides, and perhaps I can do that with this controller. No.

Robert Kaplan:

You need to be [inaudible].

Donald Silberberg:

There we go.

Robert Kaplan:

And then you need to --

Donald Silberberg:

And then this, yeah. Yup. What Kathy kindly asked me to do was to review the history of how this has all developed, and put it into a little bit of perspective, which it's a pleasure to do. And it relates very much to what Dr. Kaplan was just talking about, which is the concept of the global burden of disease. But I'm going to start a little bit before that with the Decade of the Brain, of the U.S., the decade of the 1990's.

It was developed by doctors Judd, who was then the director of the National Institute of Mental Health, and Mary Goldstein, who was the director of the Neurological Institute, with the help of a couple of key senators, with the aim being to raise public awareness of brain disorders in the U.S., and to try to get more congressional funding for NIH and other institutions of government to pursue the problems. It was highly successful. It was imitated by 43 or 44 other countries -- almost every European country, Australia, New Zealand -- all did their own Decade of the Brain, and in many cases got very good results from it. And I really see that as a first major step in just sort of raising consciousness.

A next step was the -- a next step was the initiative of the World Bank that actually started in about 1988. The World Bank found itself in a position of having a loan portfolio of about \$4 billion out in the field, around the world, related to health, and yet it had no health program. Nobody was really in charge, there was no good framework for what it was they were

doing, and with the help of several foundations who were stimulating them to do something, identified three young academics to come in and, as consultants to the World Bank, try to develop some data from studies that were available. And these were Dean Jameson, and Steve Lopez, and -- I'm leaving out somebody, I'll get to in a moment. And what they did was produce a wonderful body of data that started to be reviewed in about 1990, and so that led to this first ever annual report from the World Bank that focused on health, investing in health, in 1993. This was huge. This called attention in a way that had not happened before.

At the same time, before this, brain disorders were simply not on the radar screen in any international health circles. You couldn't talk about them, nobody wanted to listen, and you know, a number of us were aware of the plight, the problem, and trying to figure out how to address it. So fortunately, as the Global Burden of Disease Statistics were developed, it emerged that a number of brain disorders were among the largest contributors. And if one looks at the actual numbers, at that point the total burden would've been about 13, 14, 15 percent, depending on how -- what your definitions are, and that's been revised up and up with further studies as I'll get to in a moment.

And so Chris Murray -- name I couldn't think of -- Allen Lopez started this wonderful series of several books dealing with the global burden of disease, all based on their 1990 study. And as I think you all know, that's been revised several times, most importantly a big effort for the 2010 Global Burden of Disease. Back in the -- about 2002, 2003, Donna Burgin, neurologist in Chicago, not -- tried to extract from the 1990 data what was the actual burden of what we would all identify as brain disorders. As neurologists, we focus more on the non-psychiatric disorders, and you can see that at that point it looked as if at least 11 percent of deaths around the world were due to brain disorders of one kind or another. And if one looks at the prevalence of what was actually going on, what was remarkable, but not surprising in line with talks that we heard this morning, nutrition had an enormous impact in producing a big part of the burden.

So around this same time, a number of international health leaders had become dissatisfied with not a good global agenda, having been developed by the World Health Organization, and formed an organization called the Global Forum for Health Research, which was active for about seven or eight years, based in Geneva, brought in health leaders from -- and funders from

the whole world, including NIH, World Bank, Rockefeller Foundations, many governments. And as part of their effort to try to develop an agenda, let it be known that they would make some funding available to people willing to try to point out what kinds of work needed to be done, where the emphasis should be.

So I took advantage of that and was able to get funding that I was able to take to the Institute of Medicine that became the 2001 IOM report, and from the title of it you can see some of the struggles that went on. We ended up calling it neurological psychiatric and developmental disorders, because nobody could agree about mental health versus neurology versus brain disorders, so we simply said okay, we'll just use the names of those two specialties. And it was a little struggle to get developmental disorders in there. The adult-focused members of the committee at first weren't too sympathetic, but I sort of insisted that had to be, and I'm pleased that it worked.

Maureen Durkin was a member of the committee. I'll show you a couple of her illustrations that she developed for the study that are from multiple sources, just to -- as part of the motivation for moving forward. For example, in looking at the prevalence of severe mental retardation, one can see that the figures are five, eight times higher for low-income countries than for higher income countries. And obviously everything between the top and the bottom represents opportunities for prevention in some way. So enormous, enormous problem. Same thing for cerebral palsy -- that's of course a wastebasket term -- but motor difficulties due to developmental issues, again, a horrendous difference between low and middle income countries, particularly low income countries and wealthy countries. So tremendous motivation to find out what this is about and how to establish ways of prevention.

The -- one of the funders for the study -- what we had to do was go to NIH directors to get additional funding over and above what the Global Forum had given us, and several institutes contributed generously. One of them was the Fogarty Center. Jerry Hirsch [spelled phonetically] was the director at that time. He was, I believe, primarily an infectious disease gastro-neurologist person, didn't know much about the brain professionally, and I think he was quite taken at what it was that was being described, and that led him to, with Kathy Michels' help, organize a conference about the subject as a way to moving forward to developing what became the Brain Disorders Across the Lifetime Program.

And you've heard about how well the program has done. This little paragraph is from the current website of the Fogarty Center Global Health Matters, and I think the figures speak for themselves. It just has been extraordinarily successful. Dr. Martin mentioned the 2010 Global Burden of Disease study, and showed some of the slides, and I'm showing this not for any details, but just to show how sophisticated and how fine-grained the studies have become as the studies have gone on.

It leads to a couple of questions. One is, you know, what is the actual global burden of neurological psychiatric and development or brain disorders? Brain disorders a little tricky, because I have friends who study peripheral nerve in developing countries, and so that's not brain, it's connected. But using this term, it depends a lot on, what do we include? And for example, are we talking just about disorders of the nervous system -- Alzheimer's disease, for example -- that happens from within? Or are we talking about also disorders that affect the nervous system, such as cerebral malaria or cognitive disorders from malnutrition.

So if you begin to put all of that together -- I don't know what the actual figure is, but it's at least a third. Dean Jameson thought 35, 40 percent last time I talked to him about it. If you really put all of this together. Another fact that has become increasingly apparent as studies have moved forward is how extraordinarily complicated it is to find answers. And again, this is a Maureen Durkin slide that she put together for another meeting, just to illustrate the many risk factors that we all face before, during, and after birth through development, and the variety of interventions that are available, not sufficient, but that is much of what's available. And if you can use this kind of schema to illustrate the complexities and just about any of the issues that are being faced. The next step, of course, is the Brain Initiative. And I've just put up one illustrative picture of individual neurons being color-coded by imaging techniques and living animals that are going to take us to a whole next phase. So it's clear that the research opportunities are going to come from the most basic bench to the most sophisticated clinical research. I'm going to show this slide that I put together originally for presentations at the World Bank, which is why you see it up on top with NIH below. And I think that's appropriate with NIH being the support for almost all of this work that's going on until other funders become more active until other agencies really get fully aboard. If one thinks of the brain being threatened by all of the --

these possible terrible events, it's up to NIH, up to universities, up to NGOs, up to many institutions, to try to protect it.

So I'm going to go from that to a little bit different view of the issue of how to go from data to policy to try to highlight the successes that my -- that the other speakers are going to describe. But I'm going to start by just describing what went on in Bangladesh in the 1980s. When Leslie Davidson, who's sitting here, and Maureen Dirken [spelled phonetically] and Allah Khan [spelled phonetically], then a young pediatrician in Bangladesh, began to look at -- to use the ten questions screen that they had developed to identify children with -- mostly with cognitive disorders, with cerebral palsy, in rural Bangladesh. And a strange thing happened, which was that two or three months into the study, the parents of the children who were being identified basically said, "What is this? What's going on with our children?" And marched on the capital and influenced policy in the most direct way by demanding that the government pay attention and begin to develop programs to try to help. And that led to a -- see change in Bangladesh and their way in handling this which has become -- and then at the same time, surrounding countries began to pay a little bit more attention. So I would site that within this realm of this kind of epidemicalogical research, as maybe the first success in epidemiology as translational research going from data to not bedside, but to public policy.

So in a moment I'll stop and let you hear details about these studies. You'll hear the same kind of success in India from Dr. Arora. I'll close with this. My view of the future, this is the Boat House Row on Schuylkill River in Philadelphia. And I think the future is very bright, but I wouldn't want to try to predict how it's going to play out, much like the reflection in Boat House Row. So thank you again for the opportunity to talk about this history and I think whomever does this 10 years from now will have an even more exciting tale to tell.

Neurodevelopmental Disorders in South Asia

Narendra Arora:

Yeah. Can I have this, please? Good afternoon, friends. I bring greetings from -- on behalf of the England Study Group. We are extremely grateful and thanks to NIH for supporting this study. Right from the beginning, we have taught that this study should feed into national policy and if something can be done for a program. So national trust, which is part of Ministerial

Social Justice and Empowerment, was a partner and they partially funded this study. In addition to that, Autism Speaks was also -- funded this study. So, when we look at the challenges of neurodevelopmental disorders, Dawn [spelled phonetically] has set the ball and we see the kind of alignment, which has been taking place among radius global initiatives that things gradually start taking shape. But right at the country level, there are additional issues and challenges which need to be addressed: issues of screening, most of our population has no access to and no understanding of these disorders, issues of diagnosis, issues of management. Where do you manage in a country of 1.2 billion? We have hardly seven or eight centers which are properly equipped for managing neurodevelopmental disorders, so the -- and then taking it to the scale and getting it to a public health level.

So it was with these challenges in mind, we conceptualized this study and the first objective was to identify, develop, and validate culture and context adapted, consensus clinical criteria, which could be used in the [unintelligible] environment for diagnosing neurodevelopmental disorders, develop and validate a neuro -- develop a screening tool, and finally estimate the prevalence in two to nine-year-old children. And basically we thought that this program will feed in to developing a national program. Again, we -- at England, we always feel that if the key stake holders are part of the game, it becomes easier subsequently for translation, and as a result almost all major key pediatric neurologists, developmental pediatricians, and some other prominent pediatricians and epidemiologist are part of this team. Along with this, we are six international experts and we started the development of consensus clinical criteria because the issue of diagnosis is the first one.

And we were looking for these nine disorders: hearing, learning, intellectual disabilities, speech and language, vision, autism, ADHD, neuromuscular -- neuromotor impairment, and cerebral palsy, and epilepsy. So we said in that -- initially there was suggestions that, "Why don't we go just for one or two?" But we thought since there is a total gap we should approach it. So the initial file there were existing instruments which could be used in the field area. And we -- the group decided to continue with that. But we were having difficulty with the diagnostic tools for Autism, ADHD, neuromotor impairment, cerebral palsy, and epilepsy. And for this consensus, clinical criteria was developed [unintelligible] and subsequently validated using appropriateness criteria method using Symnophidell [spelled phonetically] Technique.

And so we have these four tools and these two are based on DSM4 criteria and [unintelligible] epilepsy exporting diagnosis. And as you can see, the tools have been validated at three sites across the country. And we found that this excellent sensitivity and specificity, we were anywhere between 85 percent to 98 percent sensitivity and specificity over 98 percent most of the times.

The next was a screening tool. We started with the ten question tool, which Dr. Silberburg mentioned and the group expanded this to 39 items and we expanded the scope to include these behavioral disorders: Autism, ADHD, and learning disability in addition, because the 10 question addresses the other parameters. And these 39 items, they were overlapped and that was the kind of spectrum of which this 39-question screen tool reflected. We started with the kind of validation process. The first step was the technical advisory group had worked on it for almost through three cycles over one-and-a-half years and construct validating.

In step two, one of the important things we realized that if you develop an instrument -- if it is to be context and culture valid, then it should be developed and talked through the local language. So it was first written in Hindi, translated to English, and then to 11 other Indian languages and back translated. We thought it was a very good lesson for us. And because we were able to capture some of those expressions where we were having difficulty in English. In step three, it was validated for its understanding and sequencing issues cultural and acceptability.

And finally, in step four, we had done the rehabilitation. Thereafter we have gone into a community-based study, so the validation was done along the prevalence of the neurodevelopmental disorders in five centers across the country. This is Northern Hill region, just next to Delhi is a rural area, urban area in Gohl [spelled phonetically] in Uttar Pradesh, south and west of India, and in the tribal east which is Orletha [spelled phonetically]. A total -- we visited 4,000 households. We'd followed -- it was a cross-sectional study using published and proportionate to size sampling technique: two to nine-year-old year old children, equal number of boys and girls, and in the age group of two to five and six to nine. And after the data was cleaned, we had 3,800 plus.

Now when we started finalizing this screening tool, it was a -- it has been -- kind of a -- quite a challenge for us. But we looked at sensitivity and specificity for each of the item through regression analysis, principal component analysis. And it was interesting. There was no item which has either a zero sensitivity or specificity. So everything was getting picked up. But when we brought together through a combination, our final total was of 12 questions. And right as I said, we were planning that this tool should be used in the public health program. So-- and we thought that -- we were -- specificity will be a problem: false positives. So we asked both the field worker as well as doctor to look at the -- and to do the screening, and to see whether if we -- if in the field program if the tool is used in series if specificity can be improved. But what we found was that both in the hand of the field workers and well as doctors, it was working superbly. So tools seems to be robust and does not make a difference make difference whether the doctor does it, as does the field worker.

So this tool what we find is that if the -- I will draw your attention to this role: if the child has one -- at least one neurodevelopmental disorder, the sensitivity is 72 and the specificity is 64, so very high false positives. But if you take two questions, specificity improves. If three questions are taken as they are positive, then 93 percent. Obviously, sensitivity keeps dropping. And, as we know, most of the children with developmental disorders have more than one and there we find that the sensitivity is much better, although specificity remains the same. But this is [unintelligible], which is a -- we played and even simultaneously 10 question instrument was also evaluated along the days. And we found that even for those six disorders it was functioning around 65 percent sensitivity and specificity. So what now we find from a public health perspective and using the program, what we have taught and yet validating that component that if anybody has two or more questions that person must immediately be sent and some kind of a follow-up is required, because in this situation false positives may be much higher. Now this is the -- for unusual -- disorders and specificity, and as you can see for some of the disorders the sensitivity is pretty high like neuromotor impairment, intellectual disability, autism, and epilepsy, the sensitivity is very high but the specificity is poor across.

So, and finally, the third objective was the prevalence and we were amazed and this prevalence was taken up in terms of -- because the -- for all these 4,000 proper expert group and consensus clinical criteria was applied. So we were using the

gold standard and against that [unintelligible] thing was also and we find that rural area 18 percent, urban area 12.7 or 13 percent, hilly area 12 percent, interestingly in tribal area it was only five percent prevalence of these 10 disorders and we really do not know what is the reason. Whether children with neurodevelopmental disorders don't survive up to two years or whoever survives are better looked after. We do not really know the answers. So all at the country level around 15 percent children have this disorder and it is interesting that according to the previous census data the -- these disorders are supposed to be just about two percent. Now we have shared this whole data with the -- well the program and a new program was launched in 2013 -- February, which was called [unintelligible] National Child Health Program and it has two new components: development delay and disability and defects at birth. And in this program, all of us clinging to, as well as the consensus clinical criteria, has been incorporated as part of the program.

So what we see in the screening as part of this program, there is newborn screening, screening through health worker, community health workers and screening by mobile health teams. Their effort and now in every district an early intervention center has been setup as part of this program where this neurodevelopment disorders and other inborn manners of newborn those coming out of the newborn screening will be managed. So today already over 180 districts this program has been rolled out in the last 20 years. So there has been policy impact in terms of methodology of community screening, use of this 12-question screening tool for community screening and all diagnostic tools and consensus clinical criteria is being used for diagnosis. This is the framework of one of the early intervention centers. So we have -- we share the prevalence data of this journey with government of Indian and they launched a nationwide program and most of the products were incorporated into the program. It was a huge team as I said. Over 60 people were involved as investigators. Thank you very much.

Research to Policy: Impact at the Local and Global Level

Leslie Davidson:

That was incredible. Very exciting to hear the results of your work in a country so large to have that impact. So I'm going to follow on in the approach of talking really about going towards program and policy and I'm not going to really talk about our findings and we have posters out at number 20 -- happy to talk more. But -- so I'm going to start by talking about our study in our own impact, which was a Fogarty 20 -- R21 and then an R01

in South Africa in collaboration between the University of Kwazulu Natal and Columbia University. Then I'm going to talk a little bit about what's happening at UNICEF and then just touch on USAID in terms of what's happening at the global and residents against the research that all of you are creating.

So this part is about my coworkers, my colleagues, in South Africa and at Columbia and everything I'm saying really results from them. So Shwabe Cachali [spelled phonetically] and Mira Chagan [spelled phonetically] from South Africa, Jane Fultzfig [spelled phonetically] and Mira Taylor, none of whom could come today. Very long and very cold here, but they had other work they had to do. Shwabe [spelled phonetically] is working at the Department Of Health up in the rural areas and Mira is -- has been running the internal child health unit at the University of Kwazulu Natal in part of the result of their work in the study.

Well, so the Azenza [spelled phonetically] study which means let's make it happen. Population base cohort study of 1581 four to six years old and caregivers followed up two years later. It was set in five tribal area of the valley of 1000 hills in East Zulu population. Parea-urban [spelled phonetically] no -- almost no transportation: one main rode and a lot of foot paths, limited services, history of Apartheid poverty and equality, tribal warfare, had HIV. So at the time our children were born, 40 percent of their mothers were HIV-positive and it was actually the year in which South Africa changed their national policy of refusing to believe HIV that was a virus and they began to intervene to interrupt transmission and since 2003 they've moved on step-by-step, but now they've been ruling out a fairly massive HIV treatment and prevention program.

But our children didn't benefit very much from that. So there was a door-to-door survey. We used the 10 questions. We didn't have the benefit of the new instrument from our colleagues at INCLIN, which is very exciting. We collected information on 87 percent of the eligible children. We had household information and 10 questions and then we went on a clinical assessment, which was 88 percent of the children identified with information on prenatal, neonatal, and children and health and development. We did a physical exam, we did the same auto-acoustic commissions and tympanometry to look at hearing, vision, gross motor speech, cognitive hemoglobin, and HIV, and I lost the bottom there, which was behavior. The caregivers -- we did an abbreviated history, we assessed their mental health for reasons you heard about this morning, about the mental health of caregivers on their children, and we offered HIV testing.

So what was our goal? Well, it was with the long-term goal of intervening to change what happened to children. We were investigating how the ability of children with neurodevelopmental disorders could function cognitively and socially -- to function cognitively and socially as influenced by health related HIV, anemia, and infections. Contextual, socio-economic, environmental, access to care, and therapeutic interventions. And psycho-social factors: caregiver characteristics, including their mental health, and substance use, and family function. We were funded by NIDA; we were very lucky. So what I want, then, is to talk about how we approached this, how we began, and how that later impact what we did. And I missed my slide. There. That one. So first thing, study staff, okay.

So we hired people who were local to the area. See if this works, yes. Most were local, we trained them, and they had never done research before, so they had been to high school and none of them really had been beyond high school. We had the benefit of some mid-level psychology assessors who were non-professionals who had worked on child health and child outcomes and we trained them in adult and they were -- this really goes back to what was talked about this morning in terms of task shifting. So if you have seven child psychiatrists in a whole country and not enough doctors, you can't do research using them as your main evaluators. And so task shifting, I think, is an imperative role we are all going to be working with. Many received educational assistance for additional training. Some went to college. Some moved to social work degrees. Some moved towards occupation health and rehab, but many of them got trained as a result of the study and our two main South African study leaders I mentioned: one is in now the national position in the Department of Health and one runs the Maternal-child Health Unit as U.K. [unintelligible]. They were both Fogarty Fellows. And they both were doing their training just before the study began and now they are mid-professionals, mid-career, doing really well and training the next generation, which is very exciting.

One of the things I love and probably you do too about the way that Fogarty planned this was, we're doing research, but our goals are also to do the capacity building and shift responsibility into the other countries or start with responsibility in the other countries if you're the American. And that frame and structure allowed it to have the breadth and depth that actually moved it towards changing policy and so it

wasn't a "do the research and run." It was integrate with people into the population. I think that's a single aspect of this program that's wonderful. So what do we do with the community? Well, we consulted before the study. We consulted before the R21, after the R21, before the R01. Locally, we did the tribal authorities. We did the -- that was the two parallel governments: tribal and governmental. And we consulted with everybody. We reported back on our finding periodically through the study. We referred all the children out. We couldn't take care of all their programs, but referred them into the system that existed and figured out with the system, health system and social systems, the best way to do that. And we trained the district staff for instance, 80 of them, in the assessment of substance use were funded by NIDA. Substance use was a worry of the tribal authorities so we did a lot of trainings. We also met with the key health leaders in the area, in the district, in the province, and in the government.

And so this meant that, well, we did was referring to their needs to start with, we designed the study so it wasn't completely a community participatory approach, but it had community participation at every level. And we did that all the way through. And I think that is -- that integration, that iterative consultation, made a huge difference. The other thing we did, was we combined ethnographic with epidemiological approaches. So if we found something in the epidemiologic study that confused us or weren't sure we would go back and do ethnographic interviews to better understand it. And that integration over time gave us the power to be listening to and influence out in the communities where we worked.

And this is the main thing I wanted to share with you and get your views on when we have time for discussion. So, locally, we tried and failed to get to our 21 sidunan [spelled phonetically] intervention. It was sad but we're doing it anyway. I'm not doing it, they are. So the intervention was based on the findings. So nutrition and again not too surprising -- nutrition: there was a huge amount of stunting. Over 50 percent of the children had anemia, the mothers over 30 percent had what was a screened -- fairly screened against diagnostic criteria mental health problem, 28 percent had a PTSD. They would meet GSM criteria, six percent had major depression. This was a very high-risk neighborhood community -- huge problems. And so we put in place -- my collaborators put in place, not me, -- an intervention at the three most vulnerable of the five communities work in with infant nutrition, child stimulation, maternal support for mental health disorders. And that is

ongoing. Unfortunately without a research component, there will be some minor evaluation but that was our fourth thing was to start to intervene.

At the national level, our collaborators were able to get a whole page on developmental progress in the national road to health booklet that was used for all children. And so they had several questions at the top and then they had operational ways to ask the questions down the page. So, wrong one. So they would have the questions, which were sort of vision play and learning and then going down each age it gave you ideas of how to ask them and the basic message was ask all children. So it introduced development of children into their national agenda. Oh, I forgot. The National Director of Health Promotion for the Department of Basic Education worked with our people and they're now discussing how to introduce vision and hearing screening into early rather than later education. And the study leaders are engaged with policy planning needs and the Department of Social Development and Children with Special Needs. So the study itself became part of the dialogue with the national leaders and the ministries.

Regional research -- this is not program, but and this isn't -- we're just a tiny cog in what's a bigger wheel, but one of our wishes and those of others' in the audience is to actually stop at only north/south but actually let south/south interactions. And so the -- they put -- I didn't write that down. So there's a national -- I did put it down. Sorry. I just went out of order. So Zambia conference organized by Robert Zapel on Scion Behavioral, which a number of the Fogarty people presented at and we presented at, and then that led to a book -- which is Michael here? Michael Boivin? Hi, Michael -- which Michael is editor of, participation in the neuropsychology of children in Africa. Boivin and Girafani [spelled phonetically], the editors, which has a chapter from our work representing some of the work of Fogarty and others in Africa and Michael's work in bringing together what we now know that we didn't know 10 years ago about neuropsychology of children in Africa. Again Fogarty played a role in making that possible.

We've also been involved in spinoff projects involving Autism Speaks, trying to look at the relationship of Autism to HIV. Validation study of the CDQ, which was a screener for mental health in highly HIV-prevalent areas. We were lucky that NIDA funded us to validate a study and an instrument we were using that we were having difficulty feeling sure that it was the right thing. And those all, again, integrated into ongoing

questions which one was able then to carry forward because of the base foundation from Fogarty.

And finally, just the end. Well what's happening at the global level? We heard a little bit about USAID this morning from Rick, whose last name I can't remember, who replaced Neil Boothby [spelled phonetically]. UNICEF began to move on going beyond survival and to include disability, which includes development and what they want to do with children. This was in part with response to the CRPD, which I mentioned when I asked a ill-guided question earlier this morning, the convention on the rights of People with Disabilities and the International Causification of Functioning of Disability of Children and Youth. They then created a module based on the 10 questions, which they used in the mix three and published in 2008. For mix four, they decided to do two-level assessment that proved too difficult. They got very few. But Boutahn [spelled phonetically] carried out a two-stage assessment of -- represented of their country and now they have created a national program of their country to address neurodevelopmental disability in their children -- for the country, which they've begun to implement.

UNICEF is in partnership with the Washington Group of National Statisticians, which has actually taken something like the 10 questions, expanded it. So there's a lot of parallel things happening. Expanded it, and they're going to use that and national surveys and that's almost about to be published. Again, it relates to the some of the same constructs of the screening instrument that we've been talking about. They -- UNICEF is also developing a tool kit for assessment of children using mid-level practitioners, task shifting, using algorithms, and that will be made available to countries nationally for use and it's at a level of research informed -- good enough research. And so suddenly, in the last 10 years, the ability, globally, with help from UNICEF, has been transformed into making some of what Youball [spelled phonetically] learned and studied available as a tool kit and as a validated -- cognitively validated instrument used nationally. And that's a place which I wouldn't have believed seven years ago -- eight years ago. It's really changed. So that's the thing I'm most excited about. USAID actually partnered with UNICEF and they're about to issue a report on child survival and development, and in development they're taking a very broad view. So I think the international things that are happening that are informed by individually and by the research you've created are really exciting. And that's it.

Robert Kaplan:

Kathy, we probably need some guidance. We're running -- I know the session is timed out.

Kathleen Michels:

I wouldn't mind going a few minutes over except that for the next session we -- the first speaker in particular then has to leave to fly to the west coast, like immediately. So, if we could hold questions and there'll be posters at the reception for, you know, talks.

VII. Plenary: Frontiers in Innovation - How Research in the Developing World Benefits the Whole World

Kathleen Michels:

So if the next panel could come on up and we'll be talking about Frontiers and Innovation: How Research in the Developing World Benefits the Whole World. And the NIH moderator will be Mary Ellen Michel. And Dr. Adriana Conforto will be the first speaker.

Mary Ellen Michel:

Hello, everyone. My name is Mary Ellen Michel. And I manage the program in traumatic brain injury and stroke rehabilitation for the National Center for Medical Rehabilitation Research, which is in child health. And I was particularly struck by the content of this session that talks about rehabilitation in the context of global problems and the -- of course, the goal for rehabilitation is to improve the quality for people, whether children with hydrocephalus, young adults with traumatic brain injury, or older citizens with stroke or neurodegenerative disorders. And the panel members and the topics -- the topics certainly represent TBI, stroke, developmental disorders, the global nature of disease. And the panel members exemplify the global nature of the approach to research that is needed and treatment. So all of our panel members have extensive collaboration, and involvement, and engage in training in investigators, clinicians, and training of patients and their families. And that collaborative spirit benefits everyone no matter what your geographical location.

Stroke Rehabilitation - Research Capacity Building for LMICs

Mary Ellen Michel:

Our first speaker is Dr. Adriana Conforto, who directs a very active program in Brazil seeking new rehabilitation strategies

for patients with stroke. She is Professor of Neurology at San Paulo University and Chief of the Stroke Group and the neurostimulation laboratory. She was a Fellow in the neuroprotection laboratory at Harvard, the cortical physiology program at the intramural NINDS and at the Neurology Department at the University of Bern, Switzerland, and she is currently a visiting professor at the Cleveland Clinic. Thank you.

Adriana Conforto:

Thank you. Good afternoon. Thank you for the invitation. Just an outline of the talk, we'll start with the global impact of disability from stroke. So it has been estimated in 2010, stroke was the second cause of death and the third cause of loss of disability, adjusted life years globally. Stroke mortality has decreased in high-income countries, as well as low- and middle-income countries. And the number of survivors in 2010 was estimated in 33 million. And the survivors were faced with disability most of the time. And more than half of the survivors that are faced with disability are living in low- and middle-income countries. And the number of disability-adjusted life years lost was estimated in the hundred to million in 2010. Massively concentrated in low- and middle-income countries and despite all these facts most rehabilitation research has been done in high-income countries.

So when I was a Fellow at intramural NINDS, I worked with Leonardo Cowen [spelled phonetically] in neuromodulation strategies. The idea is to try to interfere on excitability in the brain and try to potentiate plasticity processes that are adaptive that can led to beneficial improvements, especially motor function. So we can use techniques of brain stimulations, such as transcranial magnetic stimulation, transcranial direct current stimulation, but also we can work with enhancement of sensory input by stimulating peripheral nerves. And the idea is to change excitability of the motor cortex using this kind of enhancement of sensory. And at the time I was a Fellow, we did a study that showed preliminary evidence in favor of beneficiary facts of this kind of intervention in patients in the chronic phase after a stroke. At that time, we found that greater intensities of stimulation were associated with greater effects. So when I went back to Brazil, we applied for our 21 grant and the idea was to evaluate the effects of this kind of sensory stimulation in patients at a subsacute stage after a stroke at a time when plastic processes are more active. And our hypothesis was that we would get greater effects. And to our surprise we got different results. Actually, lower intensities of stimulation were more beneficial at this stage. And this study

highlighted the importance of tailoring neuromodulation interventions according from time from stroke. So plastic processes are very different in different times after lesion onset, excitability changes and we have to adapt protocols according to this variable.

But importantly, this R21 allowed us to build basic infrastructure that led to other projects, that led to involvement of trainees in the laboratory, and this led to publications. And one thing that we found difficult in Brazil was to get patients to participate in the protocols. Not because they didn't want to. Most of them really wanted it very much, but they had a hard time going to the hospital. Public transportation that is adapted to patients with disabilities is not widely available in Brazil. So we designed a kind of stimulation that could be used at home and that led to this last publication here.

And then, talking about building your research capacities, so we're in Brazil: the country with the highest incidences of stroke in the Americas. It's a large country. Stroke is the first cause of death there. And we're based in San Paulo: a large city with an estimated population of 20 million in its metropolitan area. And we're in the largest hospital in the city and in the country. So numbers of patients with strokes were not a problem for us, but there were some challenges that we had to face. So probably the hardest challenge was really the Brazilian bureaucracy. So the grant was -- we actually got it in 2004 but it took more than a year before we could recruit our first patient because of the number of Brazilian approvals that were required for us to actually start the protocol.

So just to summarize, we had a number of variables to deal with. Human resources -- this variable was and still is a big challenge. So, there is limited funding for training and we have to train researchers in the number of subjects that are important for them to be able to do the work. And also, there is a need to enhance and stimulate critical thinking, leadership, and trainees are often worried about prospectives after their -- they finish their training because academic positions are scarce in the country. And that of course impacts on their motivation to participate in the research protocols. And we address some of these issues in the current G71 planning training grant. Space was also difficult to get. It's very competitive in our situation and the only reason that we got the space to start the laboratory was because we had the R21 grant. And after we had the space and the hospital actually renovated

rooms for us to start the laboratory, then we started to apply local funding agencies and got more equipment and got the research going. In terms of patients, so we have lots of patients. And I invite you to look at poster 81 that talks about the difficulties and the differences in characteristics between patients with strokes in Brazil and in high-income countries. That this is absolutely something we have to think about when we design studies in low- and middle-income countries.

In terms of management, we had good institutional support. And the big barrier was really at a federal level, as I already said. And probably the greatest challenge today is sustainability. So after we had developed basic infrastructure, it was important for us to get other funding sources in the country. Also started to collaborate with other colleagues at San Paulo University and at other institutions in Brazil. International collaborations were absolutely crucial, so now we have an ongoing RO1 and collaborate with intermural and [unintelligible] Cleveland Clinic, Case Western Reserve University.

We also have other collaborators in the U.S. and in other countries. And this has led to more publications in the line of investigation. And I think that the main challenges for sustainability, at this point, are how to train Human Resources and the limited amount of funding that we have to attain that goal. The perspectives of a career in science in Brazil, cultural aspects that put a lot of weight on clinical duties and give limited importance to science and so we have usually very limited time to do the research. And definitely we have to adapt our rehabilitation protocols to local conditions.

So a stroke's a major global burden. We do need effective rehabilitation options for instance for motor rehabilitations that -- there is really not a lot of things we can do to improve motor hand function. So we need these new treatments and your modulation rehabilitation research is feasible but it's -- we have to face a number of challenges and we have to be creative to meet these challenges.

And I'd like to thank the NIH for all the support throughout all these years in particular. Kathy Michels for all her great support. And I'd also like to thank all my collaborators for your support and thank you for your attention.

New Neurosurgical Techniques for Hydrocephalus

Mary Ellen Michel:

I know -- Dr. Conforto is on her way to the stroke meetings, sort of, as we speak so we'll hold questions for the end. And it's my pleasure now to introduce our keynote speaker, Dr. Benjamin Warf, who is Pediatric Neurosurgeon and Director of the Neonatal and Congenital Anomaly Neurosurgery Program at Boston's Children's Hospital. In 2012, Dr. Warf was awarded a McArthur fellowship for his pioneering work on treatment of hydrocephalus in children in Uganda. He is internationally known for developing low-cost treatment for intracranial disease in children. Thank you, Dr. Warf.

Benjamin Warf:

Okay. It's a great honor to be here and I thank you and others for the invitation. The main message that I would like to leave you with today is that great need brings great opportunity. And the subheading for this is how Uganda is teaching North America about hydrocephalus.

When my family and I first went to Uganda in 2010 to help start a pediatric neurosurgical hospital with CURE International, it became immediately obvious that infant hydrocephalus was the single greatest need, hence the greatest opportunity. We currently treat about 800 new infant cases of hydrocephalus per year at CURE Children's Hospital of Uganda and that's out of about 1,200 neurosurgical operations per year, so it's the biggest, single problem that we face. We demonstrated fairly early on that infection was the single most common cause of hydrocephalus. It's quite different from the U.S. We found that 60 percent of the hydrocephalus we were seeing came from ventriculitis and most of this came in the first month of life. Therefore, it was a neonatal infection problem and a very important problem, because we could treat the hydrocephalus, which I'll get to in a minute, but many of these children have significant prancamule [spelled phonetically] brain destruction from the original infection. And so this produces a huge population of children who have a cerebral palsy kind of picture. They gave me the Genius Award and I can't figure out how to use the PowerPoint. Okay.

So I don't have time to say much about this, but this is just one slide to make a point that prevention is rally important and one of the things that we're trying to persue with the help from a lot of people. This obviously isn't my area of expertise, but one of the people that has really helped in driving this is Dr. Steve Shif [spelled phonetically] who's in the audience today

from Penn State. And I really need to acknowledge his tireless efforts to try to address this issue. We've shown a few things, [unintelligible] species appears to be an important organism in these infections. We've shown that the infections peak between rainy and dry seasons, very cyclical regular manner. And we've also shown that the survivors of this disease, a third of them, are severely disabled. So it's a big, big problem that needs addressed. The burden of disease in the sub-Saharan in Africa for hydrocephalus is, we think, huge. We've figured that there's somewhere between a quarter and a half million new infant cases of hydrocephalus that develop per year on the continent. And that's partly because of the post-infectious hydrocephalus problem. But if you only treat 80,000 of these cases per year, the economic benefits are potentially enormous. We published a paper a couple of years ago looking at the economic burden and benefit of disease and we found that there are upwards of 2 million dallies averted per year if one treats 80,000 infant hydrocephalus. And depending on how you do the economic arithmetic, this adds up to \$3 billion to \$100 billion of economic burden per year for the continent. And in terms of cost to benefit ratio, the benefit of treatment versus cost of treatment is anywhere from 7:1 to 50:1. So treatment of hydrocephalus is economically important.

So how do you treat hydrocephalus in this environment? Well, for the last 50 years, we've treated hydrocephalus mainly by putting a tube in the brain and running it under the skin, down to the abdominal cavity. That's called a "ventricular peritoneal shunt." And there's two problems with that: one is shunts are expensive. The one we use here in the States can cost anywhere from \$1,000 to \$2,000, depending on the model you choose. We early on demonstrated with a cheap -- I should not say cheap, I should say inexpensive, shunt made in India that costs \$35 that there was no difference in failure or infection rates. So we can use this very inexpensive shunt system in good conscience because we can get the same results here that we can get with an expensive shunt. However, the other really important problem is that shunts are dangerous or what I should say is that shunt dependence is dangerous. In the United States, under the best of circumstances, about half of shunts have failed by at least once by two years and about 80 percent within 10 years. With an average of three shunt revisions per child, and many patients have dozens and some even scores of operations over the course of their growing up from shunt malfunctions. And often these are life-threatening emergencies in the middle of the night. Making better shunts hasn't worked. There's a five to 10 percent infection rate with each shunt

operation. And there's estimates that just the shunt business, maintaining these things, is \$2 billion per year of health care burden.

Now in Africa, it's a more difficult story, because we lack the infrastructure, we lack the numbers of experts and centers to take care of this shunt maintenance business. And so being dependent on a shunt becomes much more dangerous. There are many roadblocks to an emergency shunt revision. The older shunt dependent patient, once the fontanelle [spelled phonetically] closes, can actually die in very short order from a shunt malfunction that can't get to help. And like I said, most shunts will fail within the first few years.

We have the opportunity to start using a technique called "endoscopic third ventriculostomy" in these children thanks to a donation of an endoscope system. And this is a technique that had been around for a while. But it hadn't been used very much in infants and we felt that we really should try to push the envelope on avoiding shunt dependence under these circumstances. And what we found was what has been found by other people, and that is that infants under a year of age, the ETV procedure does not work as well as for older children and most of our patients were infants under a year of age. Nonetheless, we're able to avoid shunt dependence in some. But this need to avoid the dangers of shunt dependence really drove us to look for other options and it caused us to resurrect, if you will, an abandoned historical operation, which it had some modest success in the early twentieth century, but had been abandoned when shunts came along in the fifties and sixties. And that was cauterizing the choroid plexus. We had now better technology to do this from a -- in a less invasive way and this had never been combined with endoscopic third ventriculostomy [spelled phonetically] as a combined procedure. And because of certain reasons why we thought ETV didn't work well in babies, it was reason to think that adding plexus cauterization might improve the outcome and the success rate over ETV alone. And what we found was that there was an indeed statistically significant increased rate of success when we combine these two procedures together for infants under a year of age. The other thing that I'd like to say is that we can come to these kind of conclusions in an environment like this where we have so many patients so many patients coming through for treatment. And so volume really breeds efficiency in regard to being able to do research and being able to come up with answers.

So we subsequently had the opportunity to look at this technique under different circumstances and for different causes of hydrocephalus, we found that -- we looked at the success rate in post-infectious hydrocephalus, which you see here on the left. And it was actually less -- made less of a difference adding the plexus cauterization procedure but for other types of hydrocephalus, for instance, in the milealingouseal [spelled phonetically] population, the kids with spina bifida and hydrocephalus it more than doubled the rate of being able to treat the hydrocephalus without a shunt. We looked at ways of predicting who was likely to success over these procedures so that we could do a better job of patient selection. And we found some interesting things; such as we did an ETV and found that there was scar in the fluid space at the base of the brain, that that greatly predicted failure of that procedure. And so we started placing shunts in those patients because we knew the failure rate was high.

And then we went on to look at success of the procedure in other individual etiologies of hydrocephalus: hydrocephalus associated with encephalocele [spelled phonetically], aqueduct stenosis, dandy-walker complex, idiopathic communicating hydrocephalus of infancy. And what we found was that, really, if you used this as the primary treatment -- if your intent is to treat children without a shunt upfront, you can avoid shunts in about two-thirds of them. The way that ETV/CPC works has, sort of, a side effect of perhaps challenging some of our ways that we think of hydrocephalus in terms of how hydrocephalus is. I'm not going to get into that. But there's the possibility that plexus cauterization effectively reduced the intraventricular pulsation amplitudes and ETV absorbs these pulsations and that may be a contribution to how this works in a very compliant infant brain.

So because of the big population of patients, we've been able to answer some questions since that time. Is ETV/CPC safe? Well, yes it is. Adding the CPC did not add any mortality or infection to the ETV alone. Does abandoned or failed ETV/CPC effect subsequent shunt outcome in regard to subsequent failure or infection when a child does wind up with a shunt? This was a question that hadn't been looked at very well before. Myself and an important colleague, Abcol Carney [spelled phonetically], who's also been a partner in a number of projects, looked at this in 900 patients who had been shunted and actually found that it didn't increase the shunt risk at all. If anything, there may be a slight protective effect from future shunt malfunctions, especially in children that have had post-infectious hydrocephalus.

Is there a difference in survival between children treated with shunt placement and those treated by ETV/CPC? I had thought that perhaps there would be, that perhaps not having a shunt would lead to a lower under five mortality. In fact, we found no statistically significant difference but the reason is because these children were dying from common treatable diseases, not from hydrocephalus-related issues. And one of the things that fell out of this particular study was that there was only one thing that played into the five-year survival of this particular study group of children with spina bifida, and that was if they were referred to a community-based rehabilitation program where they got checked on once in a while, had somebody look at their general health, do a little physical therapy, do some parental education, they had virtually the same year five-year survival as their unaffected peers whereas those with no other differences between groups who were not referred back to a community based rehabilitation program in the country, had more than twice the mortality. And this was the first report actually that the WHO endorsed CBR programs can actually reduce mortality.

We looked at the same thing in children who were treated with post-infectious hydrocephalus: the children that have the certain degrees of brain injuries like you see in post-hemorrhagic hydrocephalus in the U.S. And the same thing: there wasn't a significant difference -- not a significance difference in the way the hydrocephalus was treated but then again these children were dying in higher numbers than their uninfected peers from common treatable diseases: diarrhea, malaria, malnutrition, etc. We showed the same thing in children that had been effectively treated for encephalocele, with or without hydrocephalus. Again, children dying from these general conditions, and we began to think that perhaps disabled children may be less likely to receive routine medical care after they leave the hospital in this part of the world. And this would be consistent with the WHO report on health care access for Persians with disabilities in developing countries.

Does the mode of hydrocephalus treatment effect brain development? That was an important question. It's great to be free of a shunt but if it's better for your brain to have a shunt, we needed to know that. We looked at this in a population of spina bifida children who'd been treated either shunting or treated with ETV and CPC and we found no difference in early developmental outcomes between the two procedures. In fact, those without a shunt faired a little bit better but it

wasn't statically significant. So with this information we began to try to spread this technique because we were treating children effectively without creating shunt dependence. And there did not seem to be a downside to it. And we started a division within CURE International called CURE Hydrocephalus, where we train and equip neurosurgeons from developing countries to treat hydrocephalus in this way. We so far treated -- trained neurosurgeons in about 20 different developing countries.

We bring them to Uganda to do this training because our patient volume is so high and this leads to efficiency in training. And we provide logistical support, continuing education, and quality assurance. And we're starting to try to develop a network -- a clinical research network among interested sites.

So, what's in it for the United States? I guess that's one of the things. I mean, we put dollars into these kind of global programs. And are there reasons that doing these kind of things in low- and middle-income countries might have a broader benefit. And so we'll address that question next. And going from Africa to Boston, one of the things that I figured was that results for the same congenital forms of hydrocephalus should not change with race or geography. And that goes for various causes of non-post infectious hydrocephalus, spina bifida, encephalocele, et cetera.

And this actually points to one other possible opportunity. And that is, for instance, in a hospital in Uganda, we close about a 180 myelomeningoceles a year. At Boston Children's Hospital, we may close five to 10. So, if you want to do research that has to do with neural tube defects, don't do it in the United States. Do it in a place that has a lot of neural tube defects.

One of the big differences, though, between Africa and North America is that in Africa, post-infectious hydrocephalus is a disease of poverty. Whereas, post-hemorrhagic hydrocephalus of prematurity is a disease of prosperity. It's one of the most common causes that we see of infant hydrocephalus, but we don't see that much in Uganda because premature, very low birth weight babies don't survive.

However, we have been able to show that there are similarities between post-infectious hydrocephalus and post-hemorrhagic hydrocephalus such as intraventricular [unintelligible] scarring, variable subarachnoid space involvement, aqueduct obstruction, etc. There had been some sparse literature on

looking at ETV for treating post-hemorrhagic hydrocephalus with very poor results.

However, the status of the cistern in the fluids at the base of the brain hadn't been paid attention to before. And as it turns out, the lessons we learn from PIH post-infectious hydrocephalus in Uganda were valid for posthemorrhagic hydrocephalus in the U.S., such that children that have a clean cistern are likely -- are likely to benefit from this. And we can predict that by MRI. I'm almost done, but thanks. The blinking -- I'm sorry.

So, briefly we've looked at this in the last four years in Boston in 82 infants. And we found very similar results. We've been able to avoid shunt dependence in about 60 percent of all comers that would have gotten a shunt otherwise. And if you multiply that out by the number of shunt revisions in the cost, we've probably saved somewhere close to \$2 million or \$1.5 million in future healthcare costs by avoiding shunt dependence. And we've begun training neurosurgeons, pediatric neurosurgeons from the United States, in different centers. We bring them to Uganda to be trained by the Ugandan neurosurgeons to do this procedure because it's the best place to learn. And there is a prospective clinical trial that's now going to be beginning in North America. I'll skip the rest of this.

And I'll say again that great need brings great opportunities for delivery of health care for training not just of national surgeons, but for surgeons -- neurosurgeons in North America and also for research that can benefit everybody. Thanks a lot.

Clinical Practice: Brain Injury

Mary Ellen Michel:

Our next speaker is Dr. Randy Chesnut who is Professor of Neurosurgery and Global Health at the University of Washington in Seattle, and Dr. Chesnut is a specialist in neurotrauma. Over his career, Dr. Chesnut has directed several important clinical trials in head injury and co-authored guidelines for both surgical and medical management of brain trauma. Most recently, he is known for his work in Latin America on the management of severe TBI.

Randall Chesnut:

Thank you. I'm going to try to keep this conceptual rather than sort of basic scientific. So, I'm trying to keep the genre of the talks. The World Health Organization has estimated that trauma brain injury will surpass other diseases as a major cause of death and disability by 2020. And of course the brain doesn't care where it gets injured the Andes or the Ozarks or -- it doesn't care how it gets injured, a dog cart or a Bentley. Once it's injured, it's injured. And so it's a perfect platform for international research.

But of course in academic standards -- and academics is where you have the money, and you have the toys, and you publish. The standard of practice in managing a patient with a severe traumatic brain injury is to monitor the pressure inside the skull, the intracranial pressure, in order to guide treatment. And those of us in academic in our naivety thought that well we would just publish guidelines that would show beyond a shadow of a doubt you have to do this all the time.

Well, it turns out there is no class one literature. There is very little class two literature. And we actually couldn't do that. In addition, it's invasive, expensive, and resource-intensive. So, we actually weren't sure that intracranial pressure monitored -- monitoring made a difference. But that didn't keep us from liking it. But of course 99 percent plus of traumatic brain injuries treated in the rest of the world. And that means it's treated without intracranial pressure monitoring.

And where is the rest of the world? Well, 30 percent of people in the U.S. are treated without monitoring. Between 40 and 60 percent in Australia, Canada, and Europe are treated without monitoring. So, the rest of the world is everywhere. And, indeed, most patients will be treated without monitoring.

Now the literature is full of practices and devices in which we've developed the belief that they are effective despite the lack of rigorous evidentiary support. Belief to the extent that we are uncomfortable with testing this belief. And that was the case with ICP monitoring. None of us in high-income academics were willing to put patients in a control group where we treated them without monitoring. Indeed, none of us had ever done that. So, we thought the study was undoable. But all the way through the literature, there are stories of things we believed in and devices we were sure that worked that turns out with randomized prospective trials didn't quite work. The emperor was either unclothed or inadequately clothed.

So, it kind of came to this when it came to intracranial pressure monitoring and looking at that. And the trial was actually that intracranial pressure monitoring would be -- would result in better outcome at six months. But the interesting -- this project concept was originated by our Latin American investigators who suggested that they could do the trial because they weren't monitoring. And they were at [unintelligible]. And they were wondering if it would make a difference in their reality.

And this caught us by surprise because we'd kind of written off the ability to do it. So, this was actually a Latin American originated trial. And it was done in two countries, six centers prospectively. It tried a well-known, well-received -- it's easy to find an ICP algorithm. There are tons of them. This is the one out of head injury guidelines. And it tried that against an image in clinical examination non-ICP monitored algorithm, which didn't exist. You can't find it because again those [unintelligible] have published.

So, we had to have our investigators basically make it up so that we had an algorithm for the non-monitored people. We couldn't help because we monitor. So, this was an ad hoc algorithm. Well, the results were rather surprising. Our primary hypothesis was found wanting negative. The results at six months were indistinguishable between groups. And I didn't mean there was no benefit.

Interestingly, in contrast to the preexisting literature, none of it randomized, you were more efficient if you monitored intracranial pressure in both number of interventions and days of ICU. But the outcomes were the same. And this was not really expected but probably because in the non-monitored group we had a strict algorithm. Whereas most studies are just treat as treat can.

Now this resulted in what I think is Fogarty's first lead New England Journal article publication last December. And that's pretty cool. But what's even more cool is I think this is the first New England Journal lead article that's ever been published where the concept was originated by investigators from low- and middle-income countries. Now this has caused a lot of controversy among the academics, of course, because experience is what you get when you don't get what you want. And it's really made quite a dent in thinking about what we do.

And, of course, a lot of people have an opinion without actually reading the article. And those have ranged pretty widely from Latin America, "it's not relevant to me" to "oh, good I don't need to get up in the middle of the night anymore." And of course it's a balance. And that's as academics been our goal for the last year is to try to get people to read the article and interpret it properly.

But what did it mean to our Latin American investigators? Well, interestingly, we polled them just before we cracked the results. And they all believed it made a difference. They all believed it was going to be beneficial. So, what happened when they saw the results? Well, first of all, they were surprised just like we were that it didn't because bright, shiny objects always make people better. If you're a Monty Python fan, it's the machine that goes bing.

And they were also reassured because these people worked very hard to take care of these people in resource-limited environments. And this study showed that they were doing a good job that people were doing well in those environments with the treatment they afforded. And finally pragmatism -- it's expensive to setup these monitors. And maybe there are other places where these resources might go first.

Now Perry Pasu [spelled phonetically] in this study, we actually formed a standard of care by publishing the only tested algorithm for treatment of patients without intracranial pressure monitoring sort of by accident, but we ended up doing it. And that's our current project also funded by the Fogarty. And that is looking and trying to develop an evidence-based, as much as possible, algorithm for optimizing this monitoring because you remember our previous algorithm was ad hoc.

This current group -- this current study involves two groups, one prior exposure group, our previous investigators, and one no exposure group sort of business as usual take your brain injury. First half of the project will be data collection from that. At what point we're going to try to form a consensus-based, evidence-driven set of guidelines which will involve the evidence that we've acquired already as well as a delphi process to come to a consensus about an acceptable way of treating these based on the experience of the people who have the experience those in low- and middle-income countries. We will then test the new algorithm in both groups.

And we hope that by testing within and across groups, we can control for general protocol effects, because just adding a protocol has a Hawthorne effect. And the relevant benefit of the two algorithms so that in the long run, we can come up with optimized form of treatment of patients without intracranial pressure monitoring. Again, hopefully usable in 99 percent of patients in the world.

So what's this benefit of this whole program? Well, the high-income countries -- it's caused us to rethink our research agenda and the way we take care of people. What is the true role? It's not that we need to discard ICP monitoring, but we didn't quite have it right. Low- and middle-income countries have demonstrated that organized severe traumatic brain injury care is effective with limited resources.

And globally, it's caused us to rethink our care and ask what really is truly important. Going to low income countries, we can test things that we accept here perhaps without evidence. And it's a great balance between the two. Head injury is shared. It's never going away, and it's a global problem. And by cooperating across these borders with comparative effectiveness research, we can come to a better understanding of what we do.

In terms of capacity building, we're now up to 13 intensive care units that are doing research with us in our current project. Several of my research colleagues have spun this off into their object of work and have formed a CRO within Latin America, not only to keep our research going, but to also help other researchers and other projects go. And hopefully this is a self-sustaining organization. As well, the Latin American Brain Injury Consortium has benefited from this. And we are now putting on -- they are now putting on yearly and a neurotrauma meeting specifically focused on Latin America.

Now as presented at the beginning of this, the biggest issue here is a lack of a research culture. You're making researchers as you're doing research. It's a bit like building a bridge as you're driving across it. And that's really a work-in-progress. We need to integrate the idea that research is not what you read in a journal. It's what you do into the educational process and into the machinery of medicine in low- and middle-income countries. That's an educational process as well.

But as Dr. Conforto said earlier, another part is the funding bit. Self-sustainability requires sources of funding. And we

can't always just count on the U.S. We need to develop some sort of an internal funding to keep these researchers going once they've been trained. Some countries Brazil, Chile, maybe Peru coming along are developing mechanisms for that. But in general, it doesn't exist.

And then of course the vagaries of working in low and middle income countries. I think we all know these. And someday hopefully we'll have CROs such as Seq in all the regions of the world run by graduates of this group that can help facilitate these processes.

So, I think that head injury is a particularly easy one to study. It's a global problem. And it benefits from work on both sides. And the results benefit both sides. And so I think it's -- I'd like to thank the Fogarty particularly and my investigators and co-investigators in Latin America for making this possible. Thank you.

Mary Ellen Michel:
Our next speaker -- thank you, Randy.

Rehabilitation: Computers and Cognitive Function

Mary Ellen Michel:
The next speaker is Dr. Michael Boivin. He is professor and research investigator in psychiatry at the University of Michigan. He's been a Fulbright research scholar to the Democratic Republic of Congo and Uganda. And he has worked since then in Uganda addressing the neurocognitive effects in children with infection by HIV and malaria. He's author of many publications already cited today on neuropsychological assessment and treatment of African children. Thank you, Dr. Boivin.

Michael Boivin:
I pity the poor presenter who has to follow a Randall Chesnut PowerPoint. I'm telling you. Well, we've looked at the use of computer games with children surviving severe malaria, both severe malaria anemia, and cerebral malaria as well as children with HIV. And I'll share some of those findings -- most recent findings with you.

But first I'll begin with this adage that applies plasticity is a double-edge sword leading to both adaptation and vulnerability. And really the basis of using computer cognitive games for systematic rehabilitation with these at-risk children

is to see if positive neuroplasticity can be exploited through early to middle childhood. And perhaps throughout the lifespan to heal brains.

Computer cognitive games are presented by netbooks. This is in our study clinic in Kalunga, a rural area about 80 kilometers northeast of Kampala. But we do a lot of our training out in the field, hence the netbooks that are resistance to water, to dust, to shock of impact as our teams travel by motorcycle or by project vehicle into the rural areas to administer these training.

Our principle R01 study is children surviving cerebral malaria, severe malaria, anemia. Tomorrow Professor Chandy John's group will be presenting some of the most recent neurodevelopmental outcomes research with those two study populations from their R01 study. We're embedded within that study where after they finish their two year follow up of those children, then their approach for enrollment into our cognitive rehabilitation study as they reach five years of age and beyond.

We publish already preliminary findings in terms of the neuropsychological benefit of using these types of computer cognitive training with children surviving cerebral malaria. In fact, Paul Bangirana who's with me here, who I met the day after I arrived for a year in Uganda in 2003. We began working together on this. And now he's completed his doctoral thesis research with severe malaria survivors and is Uganda's first neuropsychologist.

We've also used these types of cognitive rehabilitation training with HIV infection in children. Looking at really two sources of development risk both the direct effects of the infection on the brain, central nervous system, and neural development in children as well as the more distant effects of the disease as it impacts on quality of care giving, nutritional status, well-being of children within a household.

And then most recently we've begun looking at the effects of antiretroviral exposure in prevention of mother-to-child through the third trimester on into early childhood up to weaning up to 18 months of age and the possibility that HART, highly active retroviral therapies, can perhaps undermine neural development during highly critical and sensitive periods and whether that can be remedied through later interventions of neurocognitive rehabilitation. We published some of those preliminary findings. And I'll share with you some of our most recent

findings of that study, which is now concluding in its final year.

Areas of the brain that we know are affected both by HIV and by the hypoxic ischemic effects of oxygen metabolically sensitive areas of the brain that are also highly critical in terms of memory, working memory, and visual spacial mapping, and learning in general. And so we've tried to target the particular training modules to target those areas of the brain that we know prospectively through our past 10 years of research.

Our cerebral malaria program was one of the first cohort of our 21 studies that specific areas of neurocognition that we know are -- have even after two to three years post-illness are affected in children's areas of attention, working memory. And so those are the kinds of neurodevelopmental outcomes that we're assessing before training after and then at follow up whether a year or two years later.

Twenty-four sessions of training -- a lot of clinical trial work with working memory training in children done out of Sweden by Clint Berg and others. About 24 sessions over a course of, say, three per week because we have to mitigate against their school and other commitments seems to be the point of diminishing returns. So, that's the amount the dosage, so to speak, for this kind of intervention.

We're looking really at three different intervention arms Captain's Log which is a commercially available CCRT cognitive rehabilitation therapy program that's programmable. You can use it to basically customize what particular neurocognitive skills that you want to emphasize in your training. Got a passive control group whom we do both pre- and post- and follow up neurocognitive assessment but who did not receive a computerized intervention.

And then a limited version of Captain's Log. It rotates randomly through the simplest levels of training, much like computer games that you'd find like Luminosity, say, on the web, whatever. And see if just the exposure the games and of themselves would be effective in terms of obtaining some of these types of benefits that we've documented in our prior published work.

And we're also looking at -- to the effects of our neurocognitive intervention in these principal neurocognitive domains be they sensory motor, be they psychiatric behavioral

symptoms as assessed by the principal care giver, or cognitive neurocognitive outcomes in areas that really are independent of the specific skills per se that we're testing but which we had hoped to see benefits in working memory, attention, executive function, so forth and ways in which these interface to practical, functional benefits whether they be academic, activities of daily living, social adjustment, and so on within the community.

But these are all modified by psycho social risk, the encephalopathy or biomarkers of severity of illness and its progress whether it be HIV or severe malaria, poverty, and then biological risk dating back gestationally and beyond.

So, our basic model both for our HIV neurocognitive rehabilitation as well as our malaria rehabilitation program. And in terms of the cerebral malaria of severe malaria and anemia in children these are -- we're aiming at 50 children in each of these study arms for the severe malaria group. And then a corresponding group of control children -- community controls recruited from their households.

For the severe malaria survivors, we're seeing these are box plots median third the first core in the range of scores and then various outliers that are plotted. But you get a sense here. And these are again running analysis of co-variants adjusting for quality of home environment, education, and other kinds of biomarkers that are important to control for when you're looking at neuropsychological outcomes.

In terms of conceptual thinking, presupposed that both the Captain's Log and the limited version of that really achieves significant benefits in comparison to passive controls. These are our most recent findings for the severe malaria survivors. And then for our HIV group in Kalunga, again looking at -- we're shooting for 50 children. We've now recruited our final child. We're completing training. We'll do post-training assessments. But up to the point where I had to prepare for this, these were our findings Captain's Log and limited version in our passive controls.

And again it's interesting to see correspondence in overall KBC this time composite global benefit to these children pre to post. And what's interesting in terms of how this has contributed to the science in general I know Elaine [unintelligible] who you'll hear from tomorrow with her colleague Robert Sternberg they really helped document the

importance of dynamic measures of cognition that we've talked a lot about neurocognition, neuropsychological, neurodevelopmental outcomes throughout the day.

And it's important to note that brains are designed to learn, to function, to adapt within those day-to-day physical environments and social environments. And the ability to learn to learn is perhaps the most important function of human adaptation in a developing brain. That sort of transcends all of these cross-cultural testing arguments that we sometimes get so caught up in. And the single most sensitive measures to our biomarkers of severity of illness, both in malaria and in HIV, have been the ability of these children to benefit from these neurocognitive games. The dynamic as opposed to static measures of neurocognitive performance.

And in terms of sustainability, the problem with these neurocognitive games is they're proprietary, expensive, limited, they have to be administered on a laptop. So, we've been developing our own game package at the Games for Entertainment Learning Laboratory Michigan State University, my colleague Brian Winn. His initial set of brain powered games that we first pilot tested with severe malaria survivors about five years ago in Malawi.

And since then, we've received a small grant for further development at our African village motif based. The African village looking at training perceptual memory and mapping, animal stampede visual working memory, and animal safari auditory visual working memory. And the lion we're going to take out. It tends to scare kids.

But these are really important in terms of looking at games that can be placed on smartphones, iPads. We just pilot tested these in Kalunga with our HIV-passive control children in a supplemental study this past year with 35 of those children. I didn't have the full results of those, but of the 24, we're seeing dramatic improvements in tests of variables of attention which we didn't get to see really with the brain-powered games.

And we think as we've interviewed these children -- try to do more of a qualitative assessment. How do you like these games? They like them better than the Captain's Log. And they're more engaging, and that might be contributing to these attention benefits that we didn't see in our clinical groups with Captain's Log.

So, there is a possibility of combining more engaging types of accessible games, through the web, through the internet, and then later on having those be foundational to more advanced types of neurocognitive rehabilitation training in a two-stage type of intervention procedure. We've submitted some grants to do that type of trial. We'll see how that works out.

Sure, so if you ask me if this technology is sustainable in Africa, I mean, seriously. Are you serious about that question? Because looking at the mobile network coverage, I'd have to turn the question back around. I mean, if it's not linked to this biotechnological revolution, is it sustainable? You know, I -- in terms of really fundamental change within healthcare, within assessment, within neurocognitive rehabilitation with what have you.

So, it's a simple choice for us, I think, today we can ride the quest for the technological wave led by this ICT-4D revolution, internet, communications, and technology, mobile platforms throughout Africa and the global world. Neurocognitive training they're sustainable because they're not dependent on systematic change of capacity infrastructure that are often times very difficult to achieve as those of us who work in such settings well know.

And we're at a crest of a tidal wave that's already sweeping the African continent, with or without our scientific participation, that will be driven by cultural and market forces and without sign of abatement anytime soon. We've got a full chapter on reviewing artwork in the book *Neuropsychology of Children in Africa: Perspectives of Risk and Resilience* lead author Paul Bangirana, who I mentioned his work earlier.

I want to recognize the R01 support through the brain disorders program. Also the NIMH support for our HIV cognitive rehab testing, our study team of second last week when we were with the team in Uganda without whose tireless efforts we would never be able to achieve any of this work.

And dedicate this to Sugal Pareg [spelled phonetically], a first year medical student who after that first year really was instrumental in our first pilot study of cognitive games with HIV children. And then came back with a Fogarty clinical research fellowship in his fourth year of medical school living a dream looking at neuropsychological outcomes in aging adults with HIV. The sequel to that was going to be neurocognitive rehabilitation in those adults, but he died in a tragic hit-and-

run accident in Uganda at the age of 25 in October of that year. We dedicate this to him. Thank you.

Gene Therapy in the Aging Brain

Mary Ellen Michel:

Our last speaker is Dr. Rudolfo Goya. Dr. Goya is a senior scientist of the Argentine Research Counsel and leader of the neurogerontology research group there. He has had many international collaborations with numerous publications on the basic science surrounding the neuroendocrine system's role in the aging process. His current work focuses on potential genetic approaches to therapy in the aged brain. Thank you.

Rudolfo Goya:

Well, in this short presentation, I will outline the biotechnology platform that we have established in our laboratory over the last 10 years or so. Okay. Go ahead. I don't know to give a -- okay. So, as we wanted to implement a new protected gene therapy in the brain of aging rats, we initially set up the methodology to construct a [unintelligible] vectors as a gene delivery systems. In these vectors, the [unintelligible] a single double-stranded DNA molecule where the genes necessary for vital replication have been replaced by the therapeutic gene or genes that we want to transfer to the target bearing regions of our experimental animals.

Our next aim was to incorporate the methodology to construct regulatory gene expression systems. These systems allow the gene therapist to control the levels of therapeutic gene expression in the treated cells or animals. This slide shows our system at work in [unintelligible] cultures. The upper diagram represents the genetic structure of one of the [unintelligible] vectors that we have constructed. In its default condition, the system is active and expresses the gene for a green fluorescent protein as you can see here in the culture. And the gene for the [unintelligible] peptide [unintelligible]. When we add the antibiotic Doxycycline to the culture it binds to our unitary protein of the system and turns transgene expression off as you can see here for GFP.

You seen some of these tools we were able to successfully implement neuroprotective gene therapy in the brain of aging rats. Time is too short for me to describe those results. However, I have brought a few copies of our recent article where

we would review our results and the results from others on this topic. So you can pick up a copy at poster 27.

This slide outlines our current biomedical goal. We want to implement several programming in order to generate [unintelligible] cells or cardiomyocytes from mouse fibroblasts. The story of [unintelligible] programming began in 2006 when Takahashi and Yamanaka reported that the transfer of a limited number of [unintelligible] genes to a mouse fibroblast was said to reprogram the cells taking them to a stage in which they behave as embryonic stem cells. This seminal study opened an horizon of previously unimagined possibilities for the development of personalized regenerative medicine. These induced a report in stem cells as they are known can be redifferentiated into different somatic cell lineages, as you can see here. And more recently has been reported that some of the Yamanaka genes can be used to directly convert mouse fibroblasts to [unintelligible] cell or cardiomyocytes in a process known as transdifferentiation.

We are presently constructing an [unintelligible] vector which is [unintelligible] and expresses the four Yamanaka [unintelligible] genes as well as the gene for green fluorescent protein as reported. We plan to use this vector to transdifferentiate mouse fibroblasts to neural precursor cells or cardiomyocytes. And subsequently, we will use these newly generated cells to implement our genetic medicine in animal models of new regeneration of myocardial infarction.

This slide illustrates the transdifferentiation protocol that we plan to use. We will use tainted fibroblasts, we will collect the cells from baby mice and see them a culture dishes. Then two days later on experimental day two we will add to the culture our vector expressing the four Yamanaka genes and the gene for green fluorescent protein. We will continue incubation for four days at which time we will add Doxycycline to the culture to inhibit the expression of the Yamanaka genes. Since Doxycycline will also inhibit GFP disappearance of the florescence from the cells. We'll confirm that [unintelligible] gene repression has been achieved. At this stage, the cells will become epigenetically unstable. And will therefore be unresponsive to differentiation factors.

On experimental day five, we would replace the previous medium by reprogramming a medium containing either neurogenic or cardiomyogenic factors plus Doxycycline, and this will depend on the kind of cells that we want to generate. We will continue

incubation with this [unintelligible] medium and by experimental day 13 or 14 we expect to see the emergence of induced [unintelligible] according to the [unintelligible] medium that we have used patches of cardiomyocytes beating. We will collect the cells and characterize them in vitro and in vivo.

I want to close in this presentation by pointing out that the other impact of the Brain Disorders Program on our institution is difficult to exaggerate. It allowed us to -- it enabled us to fruitfully interact with American colleagues and laboratories and to build a significant biotechnology [unintelligible] capacity. Furthermore, our achievements are having a positive influence on the research [unintelligible] research community in our country and also to some extent on laboratories from other countries. We have adopted an open service policy and have therefore freely distributed our vectors to research level threes in Argentina, Brazil, Spain, Germany, Japan, and the U.S. Also, a young scientist from a number of research group in Argentina are coming to our laboratory to receive research or training in [unintelligible] technology.

This is my research group in Argentina where we are 13 or 14 persons. And this are me -- my two American colleagues and counterparts; Dr. Martha Bohn from the Children's Memorial Research Center in Chicago, and Dr. William Sonntag, Director of the Reynolds Oklahoma Center on Ageing in Oklahoma City. Thank you.

Panel Discussion

Mary Ellen Michel:

Actually, we have a few minutes now to open it for comments or questions to the panel. Are there any questions from the audience? If not, I'd just like to ask, perhaps -- each of you presented such beautiful work -- to comment on how you think your research has contributed to the local environment and how you think your contributions will be sustained over the years.

Randall Chesnut:

Well I think we have generated a lot of interest at a lot of centers in doing research. We've got a lot of people who now understand the nuts and bolts of doing it and have been slowly converted from pure clinicians to clinician and researchers. And we've also got the work that Gustav [unintelligible] have done to form a -- hopefully a self-sustaining CRO that will continue to be of benefit to that area. And, actually, maybe act as a model for sustaining Fogarty trainees in various parts

of the world as a sort of continuity basis for up-and-coming new people to get a leg up on getting over some of these problems. Again you know the hope is that this is self-sustaining. So when I decide to go skiing for the rest of my life, this maintains. And that's going to come up to continued funding and actually the indoctrination of a research culture into the educational platform.

Mary Ellen Michel:

Are you going skiing, Dr. Warf [spelled phonetically]?

Benjamin Warf:

I wish I could ski. Always looks like so much fun. We have a great group in Uganda. The place is run by Ugandans. The neurosurgeons that work out there now are Ugandans and they have a culture of doing clinical research and they need ongoing support just like anybody does. But they don't need me, and so I think that with proper -- I mean the culture is there and the need is there or the opportunity is there. So I think that's going to be sustainable going forward. I have a great deal of optimism about that.

And then in regard to these people that we've been training and equipping in other countries, we're starting to bring them together with an online database. And to start doing some very basic starting out with quality assurance and data entry but we hope to form them into a clinical research network for the future similar to what the North American Hydrocephalus Clinical Research Network has done here in North America. So the best is yet to come and maybe I'll learn how to ski.

Randall Chesnut:

Yeah, 25 years ago on my first Fulbright in the Democratic Republic of Congo, it was then Zaire, and we were looking at the effects of malaria, treatment for intestinal parasites. We did our first pediatric HIV in untreated children. There was no access to anti [unintelligible] virals at that point. And malnutrition, I mean we spent the whole year looking -- providing neurodevelopmental outcomes for a lot of different pervasive public health risk factors for kids. And I came home after a really intense year and nobody seemed interested, you know. And now today everyone from [unintelligible] docs to pediatric infectious diseases adding neurodevelopmental outcomes. So seeing that happen over the span of 25 years has been extremely gratifying. And I think that trend will only continue as we move from simple child survival, although that's

still very important, to looking at quality of life and neurodevelopmental outcomes over the long term.

In terms of both assessment and intervention I really do believe that the future is with the mobile ICT 4D revolution that is extremely -- has been extremely transformative in the low resource countries and settings. And the extent to which we can really ride that tidal wave would be the extent to which what we talk about here and now, both in assessment and then interventions will be sustainable.

Rodolfo Goya:

Well, in Argentina there are -- we may say two groups of biomedical researchers. A large group working on applied neuroscience and bioscience in general trying to deal with the problems that our country faces, especially [unintelligible] with endemic diseases or diseases related to social economic conditions. And also there is [unintelligible] or smaller group of scientists, like myself, that try to keep the country updated on the ever-evolving technologies. And we try to share these technologies when we incorporate them with other scientist in my country and also in the region, n Latin American through establishing collaborations. Concerning sustainability, well to certain extent I would say that what we have achieved can be sustained with domestic funds, maybe regional funds. But definitely because [unintelligible] and reagents are real expensive. It will be necessary for us to keep receiving from some international sources funding. Because otherwise I don't think we will be able to keep up with the modernization of our equipment and with the new technology that's always evolved and are developed. So we are doing our best but I think that we will succeed as long as we can find international funds in the future.

Mary Ellen Michel:

I just like to make one comment as funder and we are the National Center for Medical Rehabilitation Research in the Child Health Institute. Everything that has been presented today is something that's highly relevant to our programs and we intend, in the future, to work more and more with our sister agencies at NIH to provide co-funding for research. And please remember us as you move forward. And we have a comment from the audience.

Male Audience Member:

The comment is thank you all for your talks. They were fantastic. I learned a lot. Chandy John [spelled phonetically] from University of Minnesota. My question is for Dr. Warf. Dr.

Warf, you obviously look at the big picture, so as a pediatric infectious diseases specialist, my question to you is are you partnering with groups to attempt to decrease neonatal sepsis in the area you work?

Benjamin Warf:

Yeah, well, that's a really great question. And the answer is: we're trying to incorporate people who have that interest and expertise. But before we can make much progress the first thing is we just -- we really need to figure out what the organisms are and whether it's as simple as just neonatal sepsis. We think it may be.

Steve Schiff is working with another group in the western part of the country in [unintelligible] with pediatricians and epidemiology folks, Ugandans at the medical school there. And they recently published a series looking at one of the organisms in babies presenting with neonatal sepsis. And found that they couldn't recover an identifiable organism in two-thirds of the cases. And there have been similar results from a study at Macquarie. So it's really an issue of trying to nail down what the infecting organisms are. I'm not an I.D. person, this is sort of peripheral to me. But it's a huge problem and we certainly are trying to interact with the people that are treating neonatal sepsis in the region. Steve.

Mary Ellen Michel:

We have one more.

Male Audience Member 2:

Actually I was going to ask Dr. Chesnut a question because that's a fantastic study that you did. But I think if we think globally about this it also is an indictment of how we have been handling intracranial pressure in trauma in the advanced industrialized medical settings. And I would suggest that it's an utter failure, perhaps, of our present application of what we know and the technologies we have. And, again, it -- I think it might speak to why not only your suggestion of working where [unintelligible] exists and where there isn't a monolithic standard of care already that blocks that. But also makes us look at our own ability to handle intracranial pressure and trauma. I'd love to hear your further thoughts on that, because I think it links the work that we should be doing here and the work that should be studied in developing countries.

Randall Chesnut:

Well, I thank you for that comment. I think you're right on. Again, we have tons of money. We have tons of resources and we're fascinated by bright, shiny objects and we don't do the hard yards before we move onto the next thing. We're smart enough to figure out ICP. I'm sure there are sub-populations that we can identify where intracranial pressure [unintelligible] makes the difference.

But to sprinkle it on everybody to the extent of increased interventions and increased expenses is not the proper use of it. So we just didn't do the hard yards. We got enamored of it, we established it, and then we didn't go back and do the tedium and now we're getting slapped about a bit. And it's happened with Swan-Ganz catheters. We didn't give up cardiac output but we gave up the P.A. catheter I bet.

So I think it's a reality check and it's a perfect example where working across resources can kind of serve as that reality check. In the future, we do need to be more careful before we adopt new technologies. We need to set a standard above which it needs to rise before we adopt it. This kind of said, "Well we didn't quite do that in the past either." But makes you wonder if some of our randomized trials like was quoted today, the number of trials and brain injury that have failed. If our baseline treatment [unintelligible] of that treatment is flawed how can you expect to ever show a benefit from a drug or a treatment? So we really need to go back a little bit to basics. And it's a bit of our enamoredness [spelled phonetically] and resourceability [spelled phonetically].

Mary Ellen Michel:

I'd like to thank everyone for participation and for the great work you do.

Kathleen Michels:

Thank you and so it's time for a break. If you can all be back at 4:15 we'll be having a mini-symposium on frontiers and genetics -- epigenetics for the developing world.

[break]

VIII. Mini-Symposium: Frontiers in Genetics/Epigenetics

Genetics/Epigenetics: Lessons From and For the Developing World

Elena Grigorenko:

Hello. My name is Elena Grigorenko and I'm from Yale University. And it's my pleasure to introduce this panel that is dedicated to advances in genetics, genomics, and epigenetics in the developing world. Of course we've heard this -- thank you. Of course we've heard references to genetics and genomics throughout this morning and then later in the day. And even in the previous section had a very elegant illustration of the frontier of today's discussions of the potential of [unintelligible] stem cell work. So in this context my job is actually just briefly highlight if you -- seems that I find interesting -- of course they're biased and then introduce my distinguished colleagues there so who would actually present some data.

So if I may, I would like to be a little bit theoretical by pointing out these three themes that, from my point of view, emerged from the work that we all follow and read about and try to contribute to. So, again, the first theme has been discussed here multiple times already and it pertains to research opportunities that simply do not exist in the developed world. And these opportunities range from very interesting constellation, also called genetic profiles, to very interesting constellations of environments because of course genes and genomes don't exist in isolation. They are also imbedded into something, whether it's a cellular environment or an [unintelligible] environment or a cultural environment or whatever you can build it [unintelligible].

So, a second theme that has been really prevalent in the literature and the recent special issue on variation in Nature Review Genetics that highlights this idea that there is a tremendous amount of genetic variation around the world where the developed world does not exist, particularly in Africa. And then it disperse itself throughout the world in very interesting patterns that we often are not able to tap into if we work only in developed countries. What's also interesting about this concept of tremendous range of variation is that there is a huge heterogeneity, for example, on the continent of Africa. And yet pockets of very interesting patterns of homogeneity within tribal units or family units or subpopulation units of which we will be talking about -- or my colleagues will be talking about today.

And finally, the third theme, which I was sitting here listening to the previous panel to our colleagues who are actually [unintelligible] translational aspects and clinical applications in the immediate interpretation of particular techniques in

different settings. Unfortunately, I was not able to find any illustrations of that elsewhere in the world but in the high-income countries right now. So, hopefully, it will be coming, hopefully, by next year's meeting we will have some of these applications but right now there is a void of such [unintelligible] applications.

So the first point that I would like to illustrate a little, first, that pertains to the issue of power. So, I mean, you know those of us who think about this literature even a little bit knows that the issue of power in genetic studies about -- especially in genetic studies of common variation -- has been discussed multiple times over and over again. And in this situation, we can actually construct samples that are not often seen elsewhere in the developed world and actually again look for something that can be rare anywhere but can be common in this highly populated pockets in the world. In this particular piece of work we were looking at a study that Kathy mentioned before. So this particular study is study of Russian orphans and I will talk a little bit about that later.

But we by accident found this very interesting translocation that disrupted one of very interesting genes from our point of view. It's a [unintelligible] gene that is located on the long arm of chromosome 15 and being a member of the [unintelligible] family it's crucial in terms of the brain maturation. It's one of the families that works as a repellent family and acts on guidance and it's a very big family. Genes in this family are mostly big and they are highly interactive with other players such as FGFs and IGFs. And we've heard a mention of IGF before so because of highly important roles of the genes there is traditionally not that much common variation in these genes.

So when you find a rare variant, you typically go through hundreds and hundreds and hundreds of samples to find another example of the same variant or another example of any variant in this gene. And of course that is possible you know on the populations that are very well defined and are large. In this particular situation we screened many, many Russians Slavs before we actually were able to characterize the mutation and understand its role in language development.

Another very interesting theme that I think is emerging in the literature, it's this discussion of various interactions of variation again and lack of such. And I will give you an example again from our work that was actually supported by our very first [unintelligible] which we were fortunate to get in

the very first year of the program. So we kind of aged with the program in many ways. So in this particular study we were looking at a Zambian population, again it's a fairly large sample of children which is impossible to get in the developed world because approximately 40 percent of these kids are out of school.

So we have about 1,500 kids and 40 percent of them are not currently enrolled in school and either have been enrolled previously for couple of years or have never been enrolled schools. So you can see that this particular constellation of factors provides a tremendous amount of opportunities for those of us who are interested in you know the situational studies. The studies that are not predetermined by randomized designs or some other experimental manipulations. But put certain populations in situations that are you know not possible to encounter elsewhere. And what was really interesting about this particular population of kids that if you consider the distribution of scores here and this that very IQ on [unintelligible] that I questioned earlier today. So we, for better or for worse, also use IQ indicators in our work.

So on the left, you have IQ indicators and then you have this [unintelligible] participant sample then you know certification by age then certification by gender, then certification by location, urban versus rural, and then [unintelligible] by schooling. And you can see that there is a tremendous variation in performance which is clearly defined by differences and means but the variance is huge. So we were trying to understand sources of some of this variation and performance linking this variation back to genetic factors. And we have -- at this meeting we have three posters presented by my junior colleagues today, tomorrow, and the day after and Sasha's poster is about linking variation in academic performance to genetic variation when kids are submerged in this very unusual [unintelligible] conditions.

And the final beat which I just mentioned and well kind of -- we want to give the podium to the -- my colleagues, pertains to epigenetic [unintelligible]. This is a very interesting, growing field of research. It's important to realize that the majority of work in animal [unintelligible] right now is done on [unintelligible] rather than [unintelligible] or some other epigenetic modification [unintelligible] epigenetic mechanisms that are not very well studied in humans yet. There are very few examples of the role of epigenetic mechanisms in human

development, in [unintelligible] development, in our physical development.

And again many, many examples, this is very recent review of [unintelligible] in their [unintelligible] cognitive processes. So we all are very excited right now in the field trying to understand what this new generation of [unintelligible] and techniques and understandings will bring to the table to those of us who are interested in understanding behavior and context and its mechanism. And I'm just going to mention briefly this particular study where we looked again under the auspices of this program and some finding the patterns of DNA methylation in children who have experienced orphan care. And again, the particular strengths of this application is that this sample comes from Russia, where the law about foster care was adopted only in 2011. So these particular kids, this sample of approximately 30 kids, have never experienced any parenting whatsoever. So they were given up to the state early on, and they experienced only institutional care.

So, this is, of course, a very unusual circumstance, but a circumstance which we were able to study. And what is also interesting about situations like that is that the main observation from this study is that the system that seems to be impacted by these early experiences most is the immune system. It's not, you know, anything that pertains to behavior right away. But it's a very early disruption that triggers a cascade of events that results in very distinct and clear patterns of behaviors.

So finally, again, we are all hoping for the best, maybe next year or the year after, when we will be discussing possibilities and opportunities of using some of this genetic and genomic findings in applied settings. And there are many possibilities in the developing world from newborns pertaining to Pharmacogenetics. Again I was not able to find any applications in the developing world.

So, to conclude, there is clearly much to research from evolution using these tools to all kinds of combinations of Gs, Es, and GxEs. And we are going to hear about working inbred population from Dr. Mansour and work on particular conditions where the prevalence of specific disorders is heightened in a particular context from Dr. Cohen [spelled phonetically]. And I would like to finish with the reference to the question that I mentioned -- that I posed myself earlier to the panel with regard to -- to the panel of directors, with regard to the

importance of understanding normative development, not only disorder development but normative development.

And I would like to echo Michael's appreciation to the program for giving us this opportunity, for once, to collect normative data on kids whom we know very little about. A couple of years ago my students and I surveyed the literature on psychology of kids from the developing world. And the English language publications dominate the field by approximately 98 percent. So we have very little published work on kids from the developing world. And I would like to state that there is going to be special issue of learning individual differences. It's an [unintelligible] journal that will be very glad to receive articles and submissions on typical development and typical development of kids from the developing world.

So with this I will turn to my distinguished colleague.

Genetic Studies of Schizophrenia in an Inbred Population

Mansour Hader:

Okay. Thank you so much. Good afternoon. Thank you for the opportunity to speak to you about our ongoing genetic research in Egypt. And we are grateful -- extremely grateful to Brain Disorders Program, which funded our earlier R21 grant and also funding the current grant about this R1 which -- the aims are mainly to map schizophrenia risk variation and consanguineous population in Egypt. And also in the meantime we'll continue research infrastructure and capacity building.

So as you know schizophrenia is a chronic common disorder worldwide. Treatment is unsatisfactory. The etiology is largely unknown, however a strong genetic component is implicated in the etiology. However, that mode of inheritance of this genetic component is fairly complex between -- I mean, which has interaction between environmental and multiple genetic risk factors. And actually, most of the gene mapping studies that have been conducted so far have been done in the Caucasian population and have used the additive model. The previous analyses also indicate the recessive inheritance. However, this approach cannot be tested in Caucasian population because there are basically outbred.

So if we look at this map that shows the prevalence of consanguinity worldwide, and almost more than one billion people have been practicing consanguinity. You can see the darker the color the higher the prevalence. You can see that the highest

prevalence rate in the Middle East, and this would be the best place to test the recessive inheritance approach. And we have done our research in Egypt, so this is the Red Sea, the Mediterranean, and this city is Mansoura, where our research is based and has been going for the last 10 years.

So, using the R20 grant mechanism we have done a case control study which shows a significant case control factor with [unintelligible] issue of 3.53. And this has been done twice, we have used the reported consanguinity as with as DNA-based data, which confirm the earlier finding.

So, since we have shown that schizophrenia is a risk -- I mean, consanguinity is a risk factor for schizophrenia, we pursued this research further to map genes for schizophrenia. So here you can see this is a typical pattern. Typical consanguineous pedigree, where this one is the patient and, you can see that the parents share the common ancestors. And we have used to test this hypothesis a technique called "homozygous by descent," which is a very powerful technique to map recessive genes. And it has been very successful in identifying recessive risk factors for homogeneous genetic disorders. So I'm going to explain to you the basic principle behind this approach.

So, basically as we know that each of us has two chromosomes, and we inherit one copy, one chromosome from each parent. However, along the process of inheritance mechanism called recombination, or shuffling, takes place where the parts of the chromosome exchanges. And as we go along, we will end up having this affected person having two copies. Those two areas on the same -- on the two chromosome, they are identical by descent and they came through the same ancestor, so through two lines of inheritance. So basically if this ancestor has a recessive risk factor, and the patient likely to inherit two copies from the same ancestor. And this area we call it HPD, or homozygosity by descent region, and if we apply this principles, we assume that these regions should be more prevalent among cases than controls.

So we have employed this in our sample and this is an ideogram, it shows a chromosome 8 region. And we looked for those HPD variations that are common in cases -- more prevalent in cases than controls. And in this analysis we have found several genomic regions, those HPD regions. But especially this one is the best result in chromosome 8, where we found eight cases that have HPD regions, mostly, I think, they are overlapping but of

different lengths and zero controls and we are expanding this further.

So, while we are doing our research we are using research to a vehicle to train and build infrastructures using the North South-South approach between U.S., Egypt, and India. We have fulfilled our recruitment, actually we exceeded our recruitment. Along the line we have trained psychiatrist, lab personnel, data managers. We have been able to establish a genetic research unit in Mansoura, which is fully functional. One of the challenges of genetic research is because of recent advances in genome-wide analysis and sequencing is how to manage and analyze the data. So we are holding weekly internet-based sessions to teach and train overseas collaborators how to handle and manage database. Thank you.

[applause]

**Genetic and Trauma-Related Risk Factors for PTSD and Depression
in South Africa**

Natassja Koen:

Thanks. Good afternoon everyone. I'm Natassja Koen. I'm from the Department of Psychiatry at the University of Cape Town in South Africa. And this is my first brain meeting and my first R21 that I've been involved in. So I'm obviously very excited to be here. So thank you for having me.

The R21 which I'm involved in is entitled "Genetic and Trauma Related Risk Factors for PTSD and Depression in South Africa." My P.I. is Dr. Dan Stein also of the University of Cape Town but unfortunately he couldn't be here, so he sends his apologies and his thanks.

Okay, so in the next five minutes I'll blitz through the significance of the research we're conducting, the importance of the research question, and the potential to advance the current knowledge base. Secondly, I'll quickly outline our methodology, our research strategy, phenotyping and genotyping methods, and our evidence-based hypotheses. We're currently -- just coming to the end of year one of the R21. So my focus is more going to be conceptual and operational, and hopefully by this time next year we'll have more meaty data to talk about. And then finally, I'll do a quick discussion of the short and long term sustainability of the grant.

Okay, so PTSD or Post-Traumatic Stress Disorder, I'm sure many if not all of you know, is a debilitating, stress-related disorder. South Africa in particular, is a highly traumatized population. However, despite our high national trauma burden, representative studies such as the South African Stress and Health Study, or the SASH, have estimated that approximately only 2.3 percent of the population experience PTSD in their lifetimes.

Now a number of studies conducted predominantly in the developed world have sought to delineate genetic or environmental risk factors which may predispose individuals to experiencing PTSD following trauma. Inheritability for this disorder is usually estimated at about 30 to 40 percent. However, many of these studies have been limited by genetic heterogeneity, by broad phenotypic definitions, and varying methodologies and by psychiatric co-morbidity. In particular, PTSD and comorbid depression have been found to be very common.

Further, few of the studies to date have really focused on the interactional effects between genes and environment in predicting PTSD following trauma. So what would we -- and in our view, our R21 provided quite a novel opportunity to investigate these interactional effects in a previously unstudied African population. Further, it's our view that by uncovering the neuro- and psychobiological pathways underlying PTSD and comorbid depression following trauma, we could actually point towards novel treatment targets and hopefully look into translational -- should I? Is that better? Okay sorry about that, is that better? And as I said focus on kind of a developing or low, middle income setting.

Okay, so looking briefly at the methodology, we've been using, ours is actually nested sub-study of a very large Gates-funded birth cohort study called the Drakenstein Child Lung Health Study, which is supporting us infrastructurally, financially, and in terms of human resources. We then managed to align with an ongoing NIMH funded study being conducted at Atlanta, at Emory University under the Piship [spelled phonetically] of Dr. Kerry Ressler. A very, very large PTSD study entitled the Grady Memorial Healthcare Study. And then, as I mentioned, we focus on trauma-related or environmental risk factors on genetic analyses, and then on interactional effects between genetic and trauma-related risk factors.

Okay, very briefly, in terms of our phenotyping methodology our participants are required to complete a battery of self-report

questionnaires, focusing on their socio-demographic characteristics, their exposure to traumatic stress, both childhood and lifetime, and then any psychopathologies which may be present. Psychopathology which have been identified on self-report questionnaires are confirmed on clinician-administered follow up assessments. And then we also ask all participants to provide a blood sample for DNA extraction. We then -- well we've now sent our first batch of extracted DNA samples to Emory, where we've elected to undertake a candidate gene approach in which we're genotyping a group of select stress related SNPs, including monoamine neurotropic, peptidergic, and HPA access-related single nucleotide polymorphisms.

Okay. I'll be very, very, very quick as I continue. So, as I said, we don't yet have analyzed data in hand, but we do have kind of a three-tiered hypothesis approach. Firstly, that a history of childhood trauma and lifetime trauma will be associated with PTSD and comorbid depression, with a dosage effect occurring. Secondly, that stress-related SNPs and PTSD will also be significantly associated, again with a dosage effect. And thirdly, that gene and environment interactions will occur, such as a combination of gene and environmental risk factors will increase the likelihood of developing PTSD and depression.

And then, in terms of sustainability beyond the current R21, capacity building is a key outcome. We're hoping to enhance low-middle income and high income collaborations as we are currently undertaking. Secondly, because we are nested in a longitudinal birth study, we do have the opportunity to follow up our study participants and to track the course of psychopathology in this patient population.

And finally, because we're also banking DNA, we're hoping to ultimately be able to do gene -- a more genome-wide association study approach. And then ultimately then our R21 will be -- will evolve into an R01 submission. Okay thank you.

[applause]

Kathleen Michels:

So, we actually managed to save nine minutes for questions.

Okay, so what are going to do now? No questions.

[laughter]

Neurobehavioral Performance in Egyptian Adolescent Pesticide Applicators

Diana Rohlman:

So this is Diana Rohlman. So you're doing these studies where you're doing genotyping and you're doing it in Egypt?

Ahmed Ismail:

Okay. Some of the genotypes can be done in Egypt. However, the GUS technique is not in Egypt yet. We have been in contact with the National Research Center in Egypt. They are planning to get the [unintelligible] platform in Cairo once this done. So we bank all our samples in Mansoura in various day laboratories. We have purchased equipment, freezers, PCR machines, QPC machines, for the bioinformatics, we recently purchased dedicated computer equipment, with 16 processors to handle this data.

Diane Rohlman:

So as far as who is conducting these analyses, are they trained in the U.S.? Are they already trained -- or is that part of the capacity building activities for your project?

Ahmed Ismail:

They're trained here, but they'll go back there and do it. So actually, the senior lab tech there, have visited Pittsburgh four or five times. Each will stay between three weeks and six weeks, almost every year. And then will go back there and he will do this, and then we'll follow this up with side visits, and do some quality control checks to make sure that everything is okay.

Diane Rohlman:

And those quality controlled checks are conducted in Egypt?

Ahmed Ismail:

In Egypt.

Diane Rohlman:

Okay, thank you.

Ahmed Ismail:

Thank you.

David Johnson:

I have a follow-up question on capacity building. I'm David Johnson from the University of Kansas, Alzheimer's Disease

Center and a new recent R21 awardee. And my question is, I think, is for Dr. Kuhn. When you're looking at the genetic effects and the plans that you have for the R01 and nested in this larger longitudinal study, what is the end that you need to find the epigenetic effects? And what sizes of samples are you thinking that you're going to be able to acquire in PTSD study? And are they sufficient to look at the interaction and how do you anticipate that unfolding in the next year or two?

Natassja Koen:

Thank you very much. There we go. I'm clearly not doing well with the mic today.

Thank you very much for that question. For the initial R21, our target sample was 500. The birth cohort study in which we're nested is currently in year two. So their target sample is 800 mom-infant pairs. The Grady Memorial study, on which we are essentially basing our methodology, they're working with 8,000. So there's obviously a very large discrepancy between what we're doing currently, and what we ultimately would need to aim for to get, you know, the causal effect sizes that you were talking about.

Essentially what we're hoping is to establish an infrastructure initially, in which we're doing kind of a candidate gene so a SNP approach. And then if we are able to broaden our sample size -- you know I'm not sure if we are going to be able up to 8,000, definitely not in the next two years -- But if we are awarded an R01 I'm still not sure we're going to be able to get up to this magic bullet of 8,000. But we definitely will be able to, for example, at least 1,000, and that would be sufficient for a SNP approach. In terms of GWAS approach you know, I'm going to have to put that up in the air.

Male Speaker:

I just had a technical question about transferring genetic material from one country to another. In one of the countries that I work in, it's actually impossible to do that because the National IRB has banned that. And there actually have been burns several times by investigators taking genetic material out of the country and then, you know, doing sort of unethical things with it. So I'm just wondering in your countries, in Egypt and South Africa and so on what the attitude of government is to transferring the national genetic material around the world?

Ahmed Ismail:

So I will speak about Egypt. I know in certain countries you -- the ban transfer of biological samples, especially blood samples, I would say of the country. Some countries they do allow to transfer DNA. We have -- we are very lucky because the School of Medicine in Mansoura, they were very successful and IRP there. And we have the H and R1 grant that we funded through the [unintelligible] Program. We have -- we got the acceptance and approval from the School of Medicine to do that. It was difficult, but it took some time to achieve that through the IRP and the School of Medicine.

Diana Rohlman:

And I also wanted to comment if I may. So our work is based in Zambia, and unfortunately my co-P.I. from Zambia, Dr. Phil Thuma is not here today, but he was at this meeting multiple times throughout the years without being funded, and he actually intentionally delayed our project and it's progress for a year, because the country banned the export of the samples. So we actually needed to ask for no-cost extension and go back to the field and you know, reach these kids and so forth, because the country -- you know there was a research drama. And they shut down the export for about 18 months. So we were just parked, doing nothing, waiting. And that paid off. So, you know, people work with an order, we exported them. And Jody, Jody you're still here [unintelligible] Dr. Fallows who overseen that expert in the lab, actually did a great job following up on that.

Natassja Koen:

Yeah, I mean, our story is kind of very similar to what we've already head.

This large birth cohort study in which my sub-study is nested went through kind of a very extensive process of getting IRB approval from the University of Cape Town which is where I'm based. Stellenbosch University which is another big South African university, and the kind of provincial KwaZulu Department of Health. So when we reach the point when we did want to send our samples to Atlanta, we did actually have full coverage to be able to do so, but it did take a year to 18 months to get that kind of full ethical approval. So, it is possible but it is a process.

Nalini Sathiakumar:

So this is not allowed in India. The Indian government doesn't allow DNA samples to leave the country and we've stuck with that for our work in India. In Egypt we've undertaken that we will

make sure that, by the end of the study, the local investigators can do everything and the DNA samples will be returned to them. Right now as Heather said, it's not possible to do this sort of give-us platforms in Egypt. So we are forced to do that work in the States. As soon as that becomes available, we'll do it there.

[applause]

IX. Mini-Symposium: Environmental Pollutants and Toxins

Kathleen Michels:

While we're waiting for everyone to come up I got another text. If anyone lost a cell phone, there's a cell phone at the registration desk.

Annette Kirshner:

Well, we'll try to do it within the time because it's been a long day. I'm Annette Kirshner. I'm at the National Institute of Environmental -- is this on? Okay. -- At the National Institute of Environmental Health Sciences, and as you've heard today, the mission of our institute is to examine the environmental exposures, the toxic environmental exposures that affect human health, and the corollary to that is -- to that, be able to provide the data to prevent these exposures.

We have -- I'm glad we followed the genetics panel, because we are very cognizant of the gene by environment interaction. And both the genetic implications of environmental exposure and the epigenetic implications of environmental exposure. A simple genetic problem would be we have enzymes that metabolize toxicants in the body. Genetically, some of us are slow metabolizers, or others are fast metabolizers. And the slow metabolizers, I guarantee you, are at great risk from any exposures.

Let's get to the panel. We have a very illustrious panel. Our first speaker is going to be Dr. Rohlman, and she is here with her collaborator from Menoufia University, Dr. Ahmed Ismail. Dr. Rohlman is at the -- recently transferred to the University of Iowa, had been at the Oregon Health & Science University prior to that, and still has connections and contacts. And the work that she has been doing in Egypt we had funded previously outside of the Fogarty Program. Dr. Anchor [spelled phonetically] and et al. And so Dr. Rohlman used it as a method to start a new project in that same field.

Diane Rohlman:

Thank you Annette. What a nice introduction. And thank you Kathy, for inviting me to come. So we're going to go back to Egypt here and, you know, Ahmed was able to join me here. Some of our other key colleagues are listed up here, but they certainly make up only a small part of the research team involved in this research.

So I'm going to give you a snapshot of our research that we're doing. I want to start off -- I do have a conflict of interest. Some of the tests and measures that I'll be talking about today are licensed to a company of which I'm a member of. This is reviewed on an annual basis and monitored. If you have more questions about that, we can talk about it after.

So, to give you some background, we're looking at organophosphorus pesticides and these are a class of pesticides that are used widely around the world. They're being phased out of the U.S. but they're still being used in a lot of developing countries. And what we're concerned with is repeated low-level exposures to these pesticides and to seeing what health effects are associated with those exposures.

We're interested in adolescents, because around the world children are engaged in agricultural activities and they're exposed to the same risk as an adult populations. However, their bodies and their brains are still developing, which we think puts them at greater risk. Pesticide application in Egypt is primarily -- what we're looking at are the cotton crop applicators. It's highly regulated by the Ministry of Agriculture, and the primary pesticide that is applied is a pesticide called chlorpyrifos. So preliminary research has found that there's high exposures in adolescent populations, we see that there's more symptoms in these groups. And we also see that there's depressed cholinesterase. Adults also have high exposures -- when we worked with the adult's applicators and pesticide workers, we see very high dermal exposures there. But what we realize is that nobody has established if these exposures are cumulative across time, and what happens to them after exposure ends, do they reverse.

So, the research goal of our study is focused on testing that hypothesis. So in our R21 study we did a 10-month longitudinal study where we began -- Let's -- there we go. Before the application period, during the application period, and after, following the adolescents and testing in multiple time points. We used various measures here; we had them complete symptom

questionnaires, we had them take neurobehavioral test batteries, which were computer and paper tests, we did medical exams, and we took blood and urine samples to measure biomarkers.

Some of our results, we see that there are very high exposures in these groups. On all of these graphs, we have the 10-month time period here. -- I can't seem to get my little pointer working. Whoops. -- Well, we'll go without it. Looking at that the shaded area shows the application period here. The two lines, one is -- the blue line is the non-applicators, the red line is the applicators. So if we look up in the upper left hand corner, we see that -- there we go. We see that, during the exposure period, the metabolites in the urine increased for both group, which was interesting to us. And then if we look at neurobehavioral performance over here, we see that there is a difference between the groups on these two measures that I have shown here. So this is a snapshot showing you some of the things we find, our poster number 55 we'll give you more information.

Let's talk about capacity building. As I mentioned, children around the world are involved with these pesticide exposures, and we feel that it's important to increase capacity at a local level, in order that local research can evaluate the impact that to these exposures. So we're doing that through a number of activities include building resources, skills training on using these neurobehavioral test methods, and using these biomarkers there. We've been successful in that the neurobehavioral methods have been used in other studies, there's mentoring and training. And we're trying to build a competitive research culture so there's a culture at Menoufia University. You need to think outside the box when you're doing these types of projects. Egypt has gone through a political revolution, which has impacted our research. So it's made it travel to Egypt difficult. So we brought the team to Dubai, and we met there in December to talk about our research.

And, next steps, we were lucky enough to be funded for an RO1. We'll continue to follow the cohort looking at the relationship between these biomarkers of exposure and susceptibility and neurobehavioral function. We know it's time to talk about an intervention for these workers, and we want to continue to build research capacity. Just acknowledge the people that are involved and here's the research team here. Thank you very much.

[applause]

**Spinoffs from BRAIN Research grants - A Cascade Effect on
Research and Training in Sri Lanka, Pakistan and India**

Annette Kirshner:

Our second speaker is Meghan Tipre. She is substituting for her mentor, Dr. Nalini Sathiakumar. And Dr. Sathiakumar has had numerous R21s, and now has an R01 on various projects in Pakistan, in Sri Lanka, in India, ranging from heavy metal exposures, mercury exposure, indoor air pollution from cook stoves, et cetera. And Meghan's going to give us an overview of all that Dr. Sathiakumar has been doing.

Meghan Tipre:

Thank you, Dr. Kirshner. Good afternoon everyone. So I'm going to talk briefly about the D43 grant under the International Training, Research, and Environmental and Occupational Health in India, Sri Lanka, and Pakistan. Some of the highlights of our work, which led to the funding of the R21 grant and the R01, and then briefly touch upon some of the spin offs of these R21 grants.

Yeah okay. I can just do it from here.

So the UAB South Asia ITr Program is a 13-year partnership between UAB, University of, Aga Khan University in Pakistan, Manipal University in India, and University of Kelaniya in Sri Lanka. As a result of this program, we have -- it has led to a significant -- sorry. It has led to research capacity building, and training capacity building in all the three institutions has led to pioneer research in the area of environmental exposures. In particular, our work in household air pollution and lead exposure in Sri Lanka and Pakistan has been responsible for successful application for the R21 projects. In further, the training program has been responsible for establishing development and establishment of two MPH programs; one in Manipal University, and the second in Sri Lanka, which is the first in the country.

So, to talk about the brain R21. This grant looks at prenatal exposure to solid fuel smoke and infant neurodevelopment in Sri Lanka, it was funded in 2010. In addition to investigating the aim of the grant, which was to look at infantile effects of solid fuel smoke on infant neurodevelopment. It has led to development of novel exposure estimation methods for household air pollution, validation of the Bayley 3 Scale in Sri Lanka which will be used for the assessment of infant neurodevelopment

in R21 and the R01. It has also contributed extensively to the body of work in HAP, along with the other studies in Sri Lanka, Pakistan, and India. And it has been -- it has led the foundation work for getting administrative supplement for our ITr program. We also were funded for a GRIP R01, a Global Research Initiative Program, looking at HAP in black carbon and an R01 that Dr. Kirshner just mentioned, expanding the R21 research. It also led to informing the policy makers about the problem in the country about HAP.

Next it was -- it served as a training base for in country MPH students and medical residents, as well as career development for young investigators. Several of the investigators on the grant are now expert advice and consultants, both nationally and internationally on HAP exposure assessment. And, last but not least, and they have provided extensive experience in grant administration for our in-country partners.

Our second R21 is looking at prenatal exposure to lead, and its determinants of environmental sources in home environment. This was funded in 2009 and it's been ongoing in Pakistan. Our preliminary work for this grant was conducted under the ITr program. We conducted a situational analysis and, followed by a pilot study, which led to the R21 project.

The key highlights of this research were application of state of the art techniques to estimate lead sources. It also highlighted the lead problem on national level, despite a banning of leaded gasoline in the country. There are several other lead sources in the country and it was informative to the policy makers. It served again as a training base for young research investigators, young investigators and also a platform for career development. The investigators on this grant provide training on several issues of conducting lead exposures to members in Ministry of Health in Pakistan, and, again, it was an extensive experience in grant administration.

So to summarize the impact of R21, it has fostered pioneer research in these developing countries, built evidence base for policy development, built in-country capacity for research and training, and spurred novel research ideas as off shoots of these grants. In fact, we have submitted two R21s last year and they are under review right now, and we'll be submitting another R01 in June. We would like to thank NIH, especially Fogarty International and National Institute of Environmental Health Sciences for their continued support, and our international partners. Thank you.

[applause]

Autism in Jamaica

Annette Kirshner:

And last but not least, is Dr. Mohammad Rahbar, who is a statistician from the University of Texas, Houston. And who is doing his study in Jamaica on autism, looking at the risk for autism from various exposures, PCBs, heavy metals, et cetera. And --

Mohammad Rahbar:

Good afternoon. Thank you for the introduction. Sorry, my back hurts. I played tennis during the weekend and pulled some muscles. It's nothing to do with sitting all day here.

[laughter]

So our partnership is with University of West Indies, and the teams -- first of all, when we were told we have only five slides. We tried to condense it, this was like 10 slides and -- sorry for lumping altogether. So I want to take a few seconds to introduce our Professor Samms-Vaughan, our collaborator in Jamaica, she's sitting here, for her leadership. That, I would say that that's one of the strength of our project, to have a good leadership in Jamaica. Thank you for making the time to join us here.

The second thing, is this that this partnership started in 2009 with an R21. So our R21 initially was funded NICHD and Fogarty, and we started in June of 2009. And we got actually two no-cost extensions, and it lasted until 2013. And we were glad to hear that our R01 from NIHS was funded in September of 2013, so, almost connecting the two. So we have been working in Jamaica for past four years.

So, I've tried to condense the specific aims of R21 and R01 together because essentially, we added some environmental toxins. Our research is essentially looking at gene environmental interaction in relation to autism. And the environmental exposures or the environmental toxins, initially we had five heavy metals; lead, mercury, arsenic, cadmium, manganese. And then, as we were conducting this project, we realized that Jamaica is the exporter of oxide, and we forgot to include aluminum into the R21. And so we added aluminum and

then we add PCBs and OC pesticides, also as part of this additional environmental exposures that we wanted to study.

The genes involved are -- the GSE gene had to do with metabolism of heavy metals. This gene is also related to detoxification of heavy metals as well. So there's enough literature about this gene's very well known, genes in terms of their role in metabolism of these heavy metals. So we have included that as part of the genes that we'll be studying. We are only studying genotypes at this point. The reviewers actually encourage us to look at heavy genetics and, because the cost of doing PCBs and other are so expensive, so we couldn't really include it. But we have the capacity to write another grant to do epigenetics in the future.

So one important thing which happened between R21 and R01 was that in 2011, Dr. Samms got funding from another source to start a birth cohort from 10,000 pregnant women during the third trimester, and follow them up to two years of life. The children -- the children were two years. So we've jumped in and in the middle of this thing. We had the opportunity to have some cold blood samples, as the children were born with money left over from R21, and then the children are expected to be followed when they are age 3 to 4, and we will be assessing their PCBs and OC pesticides, as well as the heavy metals. So this is an important cohort that really -- that our study is not completely built on this cohort, but to the extent it's possible, we will try to utilize that in part of our study.

So this is a case-control study. The cases are ascertained through standard ADI-R and ADOS. The -- one is a questionnaire, parent questionnaire, and one is observation schedule -- That these are really take long time to assess and I've observed some of this and, very tedious to assess autism. The controls are also assessed by shorter -- short questionnaire, social communication questionnaire, SCQ, to ascertain that they do not have any developmental disabilities and so on.

So there was a question earlier about the other colleagues that, when you want to do gene environment interaction, what is a reasonable sample size? The sample size for the R21 was 150 cases and 150 controls. We only knew that we will be able to detect gene environmental interactions if the effect sizes are really large, the interactions. But that does not seem to be the case, and so when we built our R01, we have actually increased our sample size to 240 cases and 240 controls. And then we are building up on the R21, so the heavy metals

component for those five heavy metals, we will have more samples. So it will be 240 cases, plus 150 that have already collected in the R21. So we are hoping that this sample size will be sufficient to really do gene-environment interaction.

But in the meantime, we have already published several papers that really I wanted to share with you. One is, there was really in the literature that some papers were saying that the age of parents, mother is important and the father is not, and age of father is important and mother is not. And when we looked at this data, our own data as well as the literature, we realized that they use these conditional [unintelligible], putting age of parents together as two separate variables, which are highly collinear, and that creates multicollinearity. And so when we analyzed through a different technique that it doesn't create multicollinearity, we showed that the age of -- all the age of parents are highly associated with the risk of autism. That has been published, and has got a lot of attention when it came out. We have published based on mercury, even though we didn't find any associations with mercury without looking at the genes yet. Because that time that we were analyzing this we didn't have genetic data.

So we found that children who have -- children in Jamaica in general, there was an association between their fish consumption and their mercury levels. And we actually identified some factors associated with their level of mercury. And Dr. Samms was telling me that she has already taken that article and taken it to the administer of Education and Health, and they are already acting on that in terms of the -- because we found certain type of seafood had high level of mercury and that, already, an action has been taking place. That's one thing about -- Dr. Samms is highly influential in terms of her relationship with the Ministries of Health and Education, and we have not had difficulty bringing the samples here, even though we need to get the license and so on. So the genetic samples are coming here, plus in terms of access to the governmental agency, it has been really -- we did not have too much difficulty.

So in terms of -- we have started the genetic analysis recently, and so one thing that we have to report with respect to genes, we have found actually a gene-gene interaction in relation to autism. We found that the GSCT1, the GSCP1, these are the two genotypes that they do actually interact and, surprisingly the alteration was then on 3. So it is a large effect that we were

able, and we are in the process of finalizing the paper and submitting for publications.

There are other papers that are coming along. So, with respect to -- one thing that in general we observing that. And we have highlight in our publication is this, that the past case-control studies in autism a lot of studies did not have the nutritional data, which is essential. Because, we found that nutrition of children is a major confounder when you analyze the case-control studies in relation to autism. The reason for that is that the cases actually have higher level of G.I. problems, and they are not fed the same food as the controls are. For example, the seafood consumption was much lower in cases than controls. And so when we were publishing our own paper, and realize that we had to control for their level of fish consumption. But when we look in the literature, people who did not have that kind of data, they made a different conclusion. And so we were wondering whether their differences were just because they could not control for the nutritional intakes of these children.

So there are several papers coming along. They are not published. So one paper has been already published on mercury and arsenic. Arsenic is another thing that we have found in actually, the soil of Jamaica there's arsenic and we are exploring. We have found an interaction between arsenic and GSTP1 I believe. And GSTP -- yeah GSTP1 and that's another observation in relation to heavy metals that we are writing the manuscript. Cadmium was another issue, there were 68 percent of children that they have levels below limit of detection, and we had to use some quanti-regression type of analysis to analyze the data. And that's another paper that we have not found at this point any associations between these heavy metals, direct relationship with autism.

So these are our publications. There's one paper on manganese, which is under review by autism research. So we have submitted and waiting for the final response. It was called minor revisions. There are several papers under preparation.

Well thank you for your attention and if you have any questions I'll be happy to --

[applause]

Panel Discussion

Annette Kirshner:

Are there any questions for the speakers? Well we could end it here, or I could drop a bomb in the laps of my panel, because we, more than any of the other institutes, wind up having a problem with the concept at NIH, that it is unethical for us to be doing studies that we know they're harmful. And would you like to see on the front page of the Washington Post that you were looking at pesticides, all that, et cetera, in a population. And we've had -- we won one argument but I wanted to ask the panel whether they have come up against this.

Diana Rohlman:

Well, I'll start off. We have had that criticism with our research is that first of all we have children who are working in a job where they're getting high exposures to a hazardous chemical, and how can we ethically do this research? And I'm going to make my response and I'll let Ahmed then say something here.

And the culture of agriculture around the world is different than the culture here in the U.S. and so we have to respect the culture, and the fact that being employed is a positive thing in many areas here. And this is going to occur, whether or not we do our research here. When we work and partner with the Ministry of Agriculture and the researchers at Menoufia University, it does provide us with an opportunity to then make changes here and to provide evidence that there are effects that they need to be mindful of. And we have been sharing results with the Ministry of Agriculture and we're working towards that in our RO1 with an intervention study. Ahmed?

Ahmed Ismail:

So, also because [unintelligible] needs [unintelligible] to manage the process of [unintelligible] application, so we need others other than those workers in the ministry. So they employ this, ever since in the summer season only to oblige with society. And so they are like part-time workers for that period only. So they overcome this, as it is illegal to make these adolescents work. So they overcome the issue by making them work in the summer only.

Meghan Tipre:

Well in our case we are looking at household air pollution and all the three countries where we been working. We've never had any problems with any ethical issues, since these countries don't see household air pollution as such a big problem yet. So in fact, the work that we've been doing, it's contributing to evidence base, to inform policy, to take these problems up at the

policy level. And go towards interventions that could help reduce these exposures, especially in women and children.

And also it is something that cannot -- it's something that it mostly affects developing countries, this problem. So I mean, at this point we are gathering, sort of, the evidence to make changes, and we haven't had any problems with this. But on the other hand, with lead studies that we did it was more beneficial because we were -- the country, again, was not aware of the problem, as they already thought that banning lead gasoline solved their problem. But after the results of the study they're more aware of the problem and are taking efforts to mitigate lead issues in the country so.

Mohammad Rahbar:

For us also I'm not aware of major issues except we have had difficulty in enrolling controls.

And so the controls are, you know, you need to draw blood and so on. So and the parents may ask, "Why do I need to give blood for this child that doesn't have any problems." and so on. So we have had those kind of things, and we have one funny story I want to share with you was, when I was reading the blogs about our paper, when it came out about the age of parents are jointly associated with autism. So some of the blog saying go and blame the parents, go and find the right risk factors. So people did not like the fact that we were saying that the older age of parents is associated with autism. So they wanted to -- us to search for better risk factors.

Annette Kirshner:

Are there any other questions that anybody would like to raise or comments? Thank you [unintelligible] -- thank you panel.

[applause]

X. Summary and Instructions for Days 2 and 3

Kathleen Michel:

Thank you everybody. So it's been a long day but we have a lot of food out there for all of you, and food you don't have to pay for.

[laughter]

So, please take a look at the posters. I'm going to finally take the opportunity myself and have some food and just really enjoy discussing among yourselves.

So we'll convene again tomorrow morning, there's not supposed to be any snow left, at 8:30 sharp we'll start. And so, please be here and we'll have any updates on the snow situation as it develops. So I think that's it. And again there still is a cell phone at the registration desk. I don't know about the earring, but so, if you've lost either an earring or a cell phone please check at the registration desk.

[end of transcript]