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PROCEEDINGS

I. PLENARY: THE "ELEPHANT IN THE ROOM": CULTURE, STIGMA AND GLOBAL NEURO-HEALTH

Kathleen Michels:
Good morning, everybody. Welcome to the second day of the Brain Disorders in the Developing World, Research across the Lifespan Symposium. I know that many of you are concerned about the storm tonight. Unfortunately we don't have any -- we didn't factor that into our plans, but since all of you are here, if NIH is open, we will have the brainstorming day tomorrow. If it's -- if there's a two-hour delay, I don't think a final decision has been made on exactly what time it would open, but that's usually what happens is either they'll have a two-hour delay or sometimes they'll close. That happens very seldom. So we'll see how this storm is playing out.

So those of you who are still here, so -- as I said yesterday, if you feel like you need to leave early or change your plans, that's -- then go ahead because we can't -- we don't know what's going to happen with the storm. But if you're still here, we're going to do everything that we can to hold the symposium. Those of you who are in the writing workshop, be in touch with us. We will have other plans even if NIH is closed. So we can probably work something out off-campus. To everybody who's still around will be working with you.

So I'm delighted to have another action-packed agenda today. And we're going to start off the morning with our moderator, Dr. Daofen Chen on the Plenary: "The Elephant in the Room, Culture, Stigma, and Global Neuro-Health."

Daofen Chen:
Thank you, Kathy. Welcome, everyone. So I'm from the National Institute of Neurological Disorder and Stroke. I'll be moderating this session, which focus on the "Elephant in the Room, Culture, Stigma, and Global Neuro-Health." And highlighting some of the social-cultural factors in the ideology prevention and treatment of the disorder to be addressed.

So we have three speakers for this session. Dr. Gretchen Birbeck will deliver the keynote speech for this session followed by two short presentations, first by Dr. Huijun Li "Mental Health, Literacy, Stigma, and Early Intervention," and then followed by Dr. Mustafa Al'Absi "Drugs, Culture, and the Story of Khat."

Now, these three speakers have one thing in common: they all are grantees of R01 or either R21 for the -- from the -- through the NIH special initiative brain disorders in the developing world. So in the interest of the time, I will introduce them very briefly as they come to the podium and get prepared and you should have the much more detailed files in your packet.

With that, let's welcome Dr. Birbeck for our first talk.

Stigma and Epilepsy

Gretchen Birbeck:
Thank you. I don't think the mic is on. Is the mic on? No.

Daofen Chen:
Just quickly, Dr. Birbeck is from the University of Rochester, where she is the Professor of Neurology and Director of Research in the Epilepsy division.

Gretchen Birbeck:
Thank you. Can people hear me?

Male Speaker:
No.

Gretchen Birbeck:
I didn't think so.

Male Speaker:
Why don't you take this?

Gretchen Birbeck:
I can. I don't think the mic's on. Oh, it is. Never mind. Sorry.

Well, thank you very much, Kathy and NINDS for giving me the opportunity to give you guys a little background about some work you've heard alluded to yesterday morning. Some confessions: I'm a physician primarily and an epidemiologist, but I'm not a social scientist, although my work has sort of made me dabble in that realm and find lots of partners who are.

Epilepsy associated stigmas has been recognized as long as epilepsy has been recognized. You can look at biblical references to it. And I'm always intrigued when you look at some of the earlier tropical medicines texts, there was a

recognition that epilepsy was particularly stigmatized in some tropical regions. In the U.S., we're very aware of this, but I think some of the more definitive actions took place when the World Health Organization partnered with the National League against Epilepsy for the Out of the Shadows campaign, which happened quite recently, in the scheme of things, in 1997.

In my, hopefully brief 15 minutes, I'm just going to give you an overview of my own experiences and how, despite being primarily a clinician, I became quite interested in stigma and stigma reduction by the cases that were presented to me when I first arrived in Zambia. The early work we did as part of our planning grant on the BRAIN [spelled phonetically] R21 that we had, the RO1 that followed, some of the broader impact that I hope our work has had in Zambia, and maybe a peak at what I think the next steps are.

I first arrived in Zambia at the end of medical school in 1994, working primarily in a rural hospital. This is a typical ward, the outside of the hospital -- and as with many rural areas, we actually have much more access to traditions healers than we do to physicians and clinical officers. In that setting, I was conducting a period-prevalence study of neurologic disorders, but I was also providing a lot of clinical care. And I think one of the values of being a clinician is, if you stay in the trenches, you learn a lot, and it can really direct your research.

So while I was trained to collect all this quantitative data, I was taking care of patients and three cases came to my attention that really made me appreciate that we were missing something in the hospital. The first was working on the pediatrics service. There were a series of children presenting, at least a week, sometimes two or three a week, who had what I called febrial seizure plus syndrome [spelled phonetically]. The staff recognized this as something they saw quite frequently and it was somewhat seasonal.

These were children presenting with febrial seizures that very severe oral lesions and a nasty pneumonia. So the seizure itself was quite simple and most children would have recovered from that, but it was very complicated by this oral burns -- turned out to be burns -- and pneumonia. And this had been going on for years. No one had questioned it very much, but because of my study I was determined to try to understand it.

And it was probably the third interview haranguing some poor grandmother who finally made the confession that the children -- that the child in her family had been given an oral bush tea that was in the home, that was intended for a person with epilepsy who lived in the home. And this was a tea that had to be delivered boiling hot and it would prevent future seizures.

Now these families were all affected by epilepsy and another family member that they had such severe fear of another incidence of epilepsy in the family, that they were taking this boiling hot bush tea and pouring it in the child's mouth while they were seizing. And what we were seeing were the burns from this and the aspiration pneumonia from this. Something that was completely mediated by fear of one more family member being affected by epilepsy. Now, we were able -- once we understood this -- to institute some education programs in the maternal and child health section, and we don't see this condition anymore. But it went on for years and years and nobody really understood it. And it was a problem -- an iatrogenic problem -- associated with just severe fear of another epilepsy case in the family.

In that same, brief, six months, I saw nine-year-old girl who was admitted to burns unit with severe burns. And it was very distressing that, in reviewing her records, she'd fallen from a tree and had a facture, she'd come in with facial lacerations, she had burns on the bottoms of her feet at four years, when we reviewed this case, we all convinced ourselves we'd missed a severe case of child abuse and we were kicking ourselves over this. It was further exacerbated by the reality that, despite this nine-year-old being the hospital, she actually had no bed-sider and nobody staying with her.

So we actually sent a social worker into the village to find out what was going on. And the social worker was completely rejected by the head man, who just said, "This child is destined to die. We can do nothing." Very puzzled. On Day 14 of the admission, the child had a generalized tonic clonic seizure [spelled phonetically], a family member was present.

They were completely non-phased. She did this all the time. She had epilepsy. All these injuries were epilepsy-mediated. The family's rejection of her was epilepsy-mediated. She'd accessed the health system several times, we never caught this. She ultimately died from her seizure-related burns. Sorry?

The last example is that we were trying to conduct a study of failure to thrive. And in doing so, what we discovered was that

the recurrent HIV-negative admissions to the failure to thrive unit, when carefully assessed, were all children who had mild cerebral palsy and epilepsy. And, essentially, when their mother had the next baby and her attention was elsewhere, these children just couldn't adequately forage to keep themselves properly nourished. With very minimal input from physical therapy, recognizing the problem, and getting another family member to take responsibility at feeding times, we were able to keep most of these children out of readmissions.

Now I mentioned I was doing this period-prevalence study at the same time, and we looked at consecutive cases of epilepsy and realized that they'd all come to attention based upon a seizure-related injury, not for their epilepsy itself. And a review of their medical records showed that only 10 percent of them had ever been treated and the doses of anti-epileptic drugs used had been so small as to be completely useless. In fact, all these people admitted only to having epilepsy only on being directly questioned. So they were in the burns unit, they were in with a fracture, and it was when you said, "How did this happen? Did you have a seizure?" that they would say, "Oh, well, yeah, as a matter of fact, I did." But they wouldn't offer that because they didn't view epilepsy as a problem that the health sector took care of.

This led us to believe that the 32 people on the registry in our [unintelligible] area of 65,000 certainly didn't represent the real burden of disease. And so, when we did a door-to-door survey, we found another almost thousand cases. And when we started offering services, 600 additional people came forward for help.

So this was a very hidden problem. So while we were trying to do all these nice biological studies of febrial seizures and neuropsychiatric problems and HIV, all of these things we were doing, we were designing it around this beast in the middle of the room -- I think elephant is too kind, I think I'm going to call it a -- the gorilla -- but we were designing all of our biomedical studies around the reality that it was so hard to study this disease because it was so stigmatized and hidden.

So when Fogarty came forward with first the stigma program and then the brain program, we all looked at each other and said, "Wow, you mean we can study this thing that we're kind of walking around desperately trying to cope with and don't really have any solutions?" And we took advantage of that and were

very fortunate that we got funded on the first round at the Stigma RFA.

This allowed us to develop a really interesting collaboration between the teaching hospital -- the university teaching hospital. We also partnered with Chainama Hills College, which is the mental hospital and the college that changed the clinical officers, including the psychiatric clinical officers, that's where most of the patients of epilepsy are referred if they make it to tertiary care. And so we thought it was very important to partner with them. And then my own rural base was one of the study sites.

We were fortunate that we worked with some social scientists early, who were able to point out to us that we didn't know enough to even know what to measure. So we started with really basic work with focus group discussions of people with epilepsy, trying to understand what the traditional healers knew and did. And we also did some CAP surveys, which included teachers, clerics, healthcare workers, and police.

The focus groups' discussions were important because they gave us a context and they helped us appreciate who were the power entities. The people that -- people with epilepsy encountered who have the potential to really impact their lives. That's how we decided -- oops, sorry -- that's how we decided -- nope, don't want to do that. That's how we decided that the CAP surveys needed to be focused on teachers, clerics, healthcare workers, and police officers.

Police officers may not be an obvious choice, but if you live and work in an urban area in Lusaka, and you have an unprovoked seizure in the middle of traffic, there is no 911 and ambulance arriving, they're going to call the police. So people in the urban areas with epilepsy were frequently encountering the police and having various experiences based upon that.

Clerics are very important advisors and community leaders, that's in both the urban and rural settings. And for children with epilepsy, the teachers have a huge determination whether those children remain in school or not. So that was why we thought that was a very important group to look at.

The focus groups of people with epilepsy, I think, were important also for the researchers. So we were all clinicians, many of us had been providing epilepsy care for more than a decade. We knew these people; that was our perspective. The

first focus group discussion, women with epilepsy, because of the distances people traveled, we would serve lunch in the middle of the day. And in the middle of the lunch, when we served the lunch, the women were all weeping because they hadn't been allowed to eat publicly and share food with anybody for year. This is how desperate their situation was. None of us knew that.

When we were trying to explore in these focus group discussions why women with epilepsy missed their visits, their health visits, the number one concern were rape fears. Rape fears? Really, where did that come from? I'm embarrassed to say that that was just some paranoia on their part. In fact, if you're a woman that has been rejected by your husband or your family of origin, your father, you are fair game in Zambia, because there are no consequences.

If a woman is raped, it's viewed as a theft and the head man will demand payment, will be approached by the male member of the family and payment will be demanded. But if you don't have a male defender, it's known, predators just know. And, in fact, when our focus groups informed our case control studies and we asked women with epilepsy about rape experiences, compared to women with hypertension, diabetes, and asthma, we found less than three percent of women with non-stigmatized disorders had experienced rape and almost a third of our women with epilepsy had.

So the peer support groups, the focus groups, were very important for helping us understand what questions we needed to ask. And then the CAP surveys were important because we customized them for the groups. And we not only asked about attitudes, but we tried to link knowledge with attitudes. So what sort of knowledge or exposure made somebody more or less sympathetic to someone with epilepsy? And we tried to quantify these things.

Ultimately, we decided that, really, the stigma associated with epilepsy has this sort of downward spiral effect. And some of those aspects are structural and some are more personal. So you have issues like -- if you have epilepsy, or your child has epilepsy, your income is lower. So your access to medical services are limited even if the services are free, you have less discretionary money to get transport to go get care.

Within a place like Zambia, the mental health sector, where epilepsy care occurs, is completely underfunded, even compared

to the main health service. So the health services existing for the stigmatized disorder are sub-optimal services. And it's just a very wicked spiral that kind of feeds on itself and it's a very difficult process to break.

When we finished our planning grant, we really felt like we didn't know everything, but we knew enough and that it was time to try and do something. So our RO1 was really evidence-based series of interventions that were aimed at a fairly small scale. So we worked out of two provinces and four study sites to try to look at some informed, very focused interventions aimed at decreasing epilepsy-associated stigma and the social and medical morbidity associated with it. So not just the stigma itself, but from that stigma stairs, like, that whole burden that goes along with it. Fairly small interventions, fairly small numbers, but focused and designed, not based upon theories, but based upon data that we had about what mattered.

Let me give you an example. We, ultimately, wanted to decrease stigma and the social and medical morbidity associated with epilepsy-associated stigma, so we wanted to intervene with some of these important groups, such as the teachers, the police officers, the healthcare workers, and the clerics. One of the important things we found from our CAP surveys were, that there are different mediators of stigmatizing attitudes. Why -- what determined whether or not a cleric stigmatized?

It was determined by whether or not that individual understood epilepsy to be a biomedical disease. If they knew that, they didn't have stigmatizing attitudes. If they didn't know that, they had hugely stigmatizing attitudes. Take-home message: you're going to educate clerics. That's what you want to tell them: this is biomedical, let's explain it to you.

Teachers, on the other hand, all understood it was biomedical. What determined whether or not they stigmatized was their personal proximity to someone with epilepsy. Did they know someone with epilepsy? A neighbor? A friend? A school classmate? If they did, they didn't stigmatize. Different intervention. So for our teachers, we brought them in for an educational program, which was kind of bogus because the intervention was that the educator was a person with epilepsy. And after three days of exposure to this person, the person came out and said, "Oh, by the way, I have epilepsy." So while the intervention seemed to be the educational piece, it was actually the exposure.

Clerics, healthcare workers. It's their comfort, it's their knowledge-level of whether they feel like they know what to do with the condition. For police officers, contagion fears drove everything. So one of our take-home messages from our work is that you can't just come up with some big social marketing campaign and think it's going to work. Different people, different entities, attitudes are driven by different things. And you have to figure that our and then you have to have focused interventions for that. So that's part of what we did.

We worked in terms of advocacy with the community leaders, but also with government leaders. We worked with the Ministry of Health. We tried to figure out some of the barriers to drunk access, et cetera. We developed some programs that were geared towards improving healthcare delivery at the secondary level, at the mental health level, at the university teaching hospital level.

Some of these things have funny side-effects. So, for instance, one of the first things that we tried to do was a drug accessibility study. And what we found was that in the last two years, the access to phenobarbitone had plummeted and we had to go back to the drawing board. Why was that? We had to go to a lot of qualitative work and a lot of interviews. And it turned out that the World Health Organization had instituted some pharmaceutical regulatory authority education plans that had gotten all of these PRAs, not just in Zambia but actually in several countries, to start cracking down on phenobarb distribution.

And so we found out what we were experiencing in Zambia was being seen in China and Argentina and all these other places, but nobody had appreciated that before. So, sometimes our study didn't get us where we thought it would, but it actually got us somewhere important. So, you know, you kind of have to go with it when things don't go the way you hope.

To date, we've put out three of the findings from our study. Peer support groups, for instance, work. They work for adolescents, they improve drug adherence, they decrease stigma. Do they work for adults? The trend was yes, but not statistically significant. And these were really basic peer support groups. These were not high level, big informed people leading them. Really, really simple intervention.

We did a costing study that showed the government that most of the cost of epilepsy care was really related to how -- they're

purchasing practices. Because that was the biggest variability and really where most of the cost differential occurred is that they bought phenobarb at the lowest price as opposed to the highest price. So, we've had a number of studies that I think have impacted local policy and have also kind of informed us about how this could be done elsewhere. And, again, I think the intervention idea of it needing to be customized is critical.

What came out of our study? Academically, I think we're quite pleased. We've got 35 peer-reviewed publications and counting and I think there's probably another five to 10 coming out of the work. This work -- somebody talked about the kind of side cascade effect. We were able to leverage the work we were doing. We were very fortunate and we got some additional funding from NINDS through a supplement that's allowed us to look at quality of care and how it changes when imaging and neurophysiology capacity comes in. We've had students that were able to get AMA funds. We had intramural dollars in an Adana Foundation Neuroimaging Grant [spelled phonetically] really grew out of this, too.

The capacity-building in Zambia has been really quite impressive. We've trained PhDs who've gone on to be research directors for the mental health sector. We're trained grants managements -- think about, talk about thinking outside the box. Anybody that's tried to move a dollar from the U.S. to another place knows how fun that is. We trained grants managers -- the best investment we could've made. And we've also been able to help the National Neurological and Psychiatric Society develop evidence-based guidelines for care as new technologies have become available, and that's been very important.

In terms of the broader scientific value, I think we've developed quality indicators for epilepsy care that are appropriate for use in low-income countries. We've gained some new insights into stigma measures and some of you may see Melissa's poster upstairs, which I think would give you some insights on that front. And I think that has implications far beyond Zambia. And then, also, we did some critical work that really linked attitudes and knowledge together and leads the way in thinking about what an interventions should look like.

I won't say it to you in the [unintelligible], but this is one of my favorite proverbs. That you can't pick nits with one finger, there are so many people involved in the work and this is just the tip of the iceberg, but it's also a lot of the fun. Thank you.

Daofen Chen:
Thank you, Dr. Birbeck. So let's move onto the next talk by Dr. Li. "Mental Health, Literacy, Stigma, and Early Intervention." Dr. Li is from Florida A&M University, where she is Assistant Professor in the Department of Psychology, the College of Social Science, Arts, and the Humanities.

Mental Health, Literacy, Stigma, & Early Intervention

Huijun Li:
Thank you very much, Dr. Chen. And also, thank you for the opportunity to share our work in China and thank Fogarty [unintelligible] and Dr. Enzo [spelled phonetically] and our program officer, Dr. Sarah Morris, for all your support.

So stigma and early intervention. In fact, stigma is a piece of a work. So I'll talk about it, but I'll focus on the other things that we do. So the topic of our research of our [unintelligible] project is broadening psychosis syndrome, investigation to different culture groups. So as many important events that happen with the Chinese people, many of the events happen at dinner tables or lunch tables and the same is true for our collaboration.

The project started when the group of researchers met in Boston and at a very good Chinese restaurant in downtown Boston. That's where we finalized our research direction. So before that, we had a lot of personal and also [unintelligible] contacts. These are the collaborative research institutions where -- the first one is where I work and the second one is where I used to work at the Shanghai Mental Health Center in China is our Chinese collaborator.

So Shanghai Mental Health Center hosts maybe the largest inpatient ward in the world. They have about 2,000 beds in the hospital and also about 100 daily outpatient visits. But there is a huge lack of research and clinical skills related to the [unintelligible] population we have in mind, which is the clinical high-risk for psychosis.

So some background information about schizophrenia and psychosis in China. So still a low- and middle-income country, although there is a rapid growth economically, research and mental health are still very weak. So we know that worldwide, the lifetime prevalence rate of schizophrenia is about one percent, in China it's about point eight percent.

So the prevalence rate is a little lower, but taking into account the large base population of -- about 1.4 billion. So China's still a country where we have the most patients with schizophrenia. It is a huge public health concern. And also, among the patients, only 30 percent receive some kind of treatment in comparison with 80 percent in the western countries.

And also, there is a huge lack of trained mental health professionals to work with patients with mental illness. For example, there is about one in 100,000 people -- one psychiatrist for 100,000 people to compare with 17 psychiatrists in 100,000 people in the U.S. Lack of trained mental health professionals. And suicide in patients with schizophrenia is also a public health concern and -- so, that's also a critical reason to think about early identification, early intervention for those who just show signs of some psychotic symptoms.

And this is natural history of schizophrenia and also illustrates where we are focusing on. So from the [unintelligible] phase to the [unintelligible] and to the first episode and then to the chronic. So as a lot of research evidence shows that the most deterioration the brain and the cognition starts at the first two years when they develop the psychotic disorders.

But even before that, some early warning signs and the function of deterioration have already started. So that phase is the prodermal [spelled phonetically], or the clinical high risk, or we call [unintelligible] risk syndrome phase. So that's the prodermal part, where we focus on. So we want to catch them early and to provide early intervention.

So these are the critical reasons to do that. Try to relieve suffering of the patients and their family and to prevent them from developing further disability, even psychosis, and, again, [unintelligible], especially in the Chinese people.

But there are a lot of barriers for us to do the early identification and the early intervention. So as Gretchen just said, stigma not only occurs to physical illnesses, mental illness is also the same, especially in China. So first, not a lot of people, even trained mental health professionals are quite aware of the early warning signs of psychotic illnesses and a lot of misdiagnosis. And, as I said, significant lack of access to services and mental health providers. And stigma --

mental illness stigma in the Chinese culture is especially damaging and persuasive for different reasons.

First, in the Chinese culture, a child -- so we're talking about adolescents and young ages, maybe age 13 and -- to 35. So they are still with -- living with family, most of them. So ideological explanations of the illness, especially schizophrenia -- what that -- is due to some misbehavior of their ancestors or misbehavior of their parents or the break-up of the family.

So for example, if the parents have a bad relationship or divorce, then that will be the causes of schizophrenia. Or they'll say it's because of excessive thinking. So they can't -- they don't have other options of kind of behavioral actions. So those are the main ideological explanations of schizophrenia in the Chinese culture.

So if we think -- if they contribute the reasons to family, so the family and the patient -- that's very devastating because the family will try to either hide the patient or the child from the public for fear that the child and the family cannot get -- will lose face. That's a key protective factor.

As a consequence, so that's -- they wait a long time to see the doctor or the psychiatrist or mental health professionals, so when they do get to the hospital, their symptoms tend to be more severe and be emergency case. And also they're afraid of their child not being able to get good job and also cannot establish a good romantic relationship. So a lot of negative kind of associations with the mental illness.

So, for the major goals of our collaborative project, one of them is to enhance the research capacity of our Chinese collaborators. And with a purpose to design the first [unintelligible] longitudinal program of research in China. And at least as some of our aims for our preliminary study. So our study is in two phases.

The first phase is to validate some clinical instruments because this study could be one of the first in China and so we needed to validate instruments and to norm them in China with the Chinese culture. So, besides, stigma, we look at neurocognitive impairment and also information processing [unintelligible] methodology and also look at psychosis conversion rate after a 10-month follow up. Also some of the risk factors for conversion.

So our project started in late 2012, so this is our second year. So, the grant is still ongoing, so we have some preliminary data to present. And -- so these are our training sessions. We provided -- when we were in Shanghai Mental Health Center. So the research to have developed skills to diagnose patients who are at risk for psychosis and some other aspects. And this is our recruitment chart. So our goal is to recruit 100 cases, now we have about 70. Among them, seven have converted to psychosis. So, again, this is early diagnosis phase. Our next project will focus on intervention.

So this is what we found in terms of the converters in terms of their clinical risk factors. As we can see, the converters tend to have a lower cognitive function and more positive symptoms. And, come back to stigma, so we did also a preliminary analysis.

We found that there was an active correlation between a stigma score and social cognition, which means that the higher level of stigma a person feels, the less likely the person is to feel comfortable in social situations, so they feel very lower self-esteem.

And these are some of our accomplishments so far. Within less than two years of our project, we had -- we just got our O1 and to continue with this line of research. And also with the training of grant writing skills, one of our major investigators got a grant from the Chinese government. And we have two publications related to our project were under review. And we do need the support of both governments to continue this line of research. And thank you all very much for your time.

Daofen Chen:
Thank you. Our next -- next Dr. Al'Absi will talk about "Drugs and Culture: the Story of Khat." And Dr. Al'Absi is a Professor of [unintelligible], Psychiatry, and Neuroscience at the University of Minnesota Medical School, where he's also [unintelligible] Chair and is the Director of the Lewis Medical Research Center.

Drugs and Culture: The Story of Khat

Dr. Mustafa Al'Absi:
Thank you. So I come from a background in psychobiology and neurobiology of [unintelligible] and therefore my presentation is going to be kind of colored by that or influenced by that. We know that drug use and drug addiction has a clear

neurobiological signature, radiated there through the reward path, the [unintelligible] back pathway, which interacts with various brain structures and brain-based processes. But we also know that the neurobiology of stuff of addiction is influenced by a host of factors: social factors, cultural, historical, geographic, environmental, and the like. Those factors lead to creating -- making the presentation of addictive behavior as well as the approach by which we can go about addressing addiction that more complex.

So this [unintelligible] born out of this complexity of social and psycho-social and environmental conditions can make this situation complicated. Now this is not unique, certainly, to addiction or to mental health. Indeed, many of the non-communicable chronic diseases are influenced by a host of psycho-social and other factors. Yet, some of us would argue that brain-based diseases are particularly influenced by psycho-social factors and therefore these factors have to be taken into consideration when addressing these problems or trying to understand [unintelligible] how they may come about.

So, and that makes the mission of program like the brain disorder program and the like that more significant in that they are important in advancing the knowledge of how -- how the brain translates these psycho-social influences in addiction and mental -- other brain-based disorders as well.

This is opportune time because we now have evolved into the [unintelligible] to some of those questions. We have multi-disciplinary -- trans-disciplinary type of approaches and recognition about the importance of things like neuro-mechanisms of these psycho-social factors. There's a field now that's growing called Social Neuroscience which addresses some of these questions. There's exciting research being done on neuro-mechanism radiating effects of stress as well as how cultural and psycho-social factors shape motivational states neurobiologically and therefore how that might promote drug use.

And, indeed, we see the neuro-mechanisms of how cultural patterns of drug use come about, attempt to influence the way these drugs effect the brain. For example, there's this notion of traditional drug use versus recreational drug use. Traditional drug use tend to occur in indigenous populations where there's access to drugs and some of this we have studied in our program.

So we were fortunate recently to be awarded a grant by the National Institute of Drug Abuse and through the program, The Brain Disorder Program, to launch what's being the first of its kind program focusing on khat. So this is a unique program that's -- that we launched a few years ago. And addressing this culturally embedded drug use in the Middle East and East Africa. And that is the plant called khat.

So khat is an amphetamine-like plant, is widely cultivated in East Africa in the Region Peninsula. It's used extensively in these regions. It's culturally sanctioned, so it's legal. And it's spreading around the world, especially among immigrant community. Until we started doing this program, we didn't really know as much about its brain effects. And just to give you a glimpse of the chemical structures that involved in the ingredients -- psychoactive ingredients in khat is called cathinone, which as you can see, structurally it's very similar to amphetamine.

The way this substance is used is usually chewed fresh -- in fresh leaves. And the person would just chew it, try to masticate the juice and swallow that. And that usually occurs in sessions individually or in groups. And the session may take somewhere between three to seven hours of just chewing. The acute effects, just like any other stimulants, start with elevation of mood and later on with kind of a more calming down and having some depressive symptoms as well as insomnia and lethargy. The cultural tolerance of this drug has led to huge escalation of drug use, especially among vulnerable populations, including children and women. In fact, some data show -- international data show that as many as 73 percent of women do or use this drug and about 18 percent of children. And so this cultural tolerance is, in our belief, going to have some cost in terms of the impacts on vulnerable population and impact on future generations.

The growing impact of this use is already being seen in terms of the impact on mental health issues, chronic diseases like heart disease, cancer, and respiratory issues. We're seeing -- one of the problems that we're seeing with this drug use is the combination or the concurrent use of other drugs, including tobacco. There's also costs to environment in terms of moving or using the land to plant -- to cultivate this drug instead of other, more important crops, as well as the taxing this has on the water resources.

So for our program, for the Khat [unintelligible] Program, we have two primary aims. The first one was capacity, building, and training. And there we've conducted multiple workshops, we've established institutional review boards in two countries -- - in two universities, we have conducted training related to ethical conduct of research, and have had a regular meeting and ongoing mentoring of our colleagues in-country. We also have been doing some research, preliminary and pilot studies, related to the cognitive affective as well as by -- behavioral effects of khat. We've done some pilot studies in primate models. We've looked at [unintelligible] issues, which is a big issue in the context of khat and other concurrent use. We've also conducted community surveys in [unintelligible] and Yemen to try to look at to the extent -- to look at the intensity of this problem and the concurrent and the [unintelligible] problems.

So far, we are -- we've published about 16 peer-reviewed journal -- articles in very well-known journals in the field, including Addiction -- European Addiction Research, and other journals. Just to highlight, two primary findings that we've obtained in our studies. The first one is that we found that chronic khat use is associated with deficits in working memory using various neuropsychological tests. We found that this seemed to be the case, particularly among individuals that not only chew but also smoke.

We also have found that chronic khat use is associated with ultration [spelled phonetically] in the psycho-biological response to stress and this is manifested by the disruption or dysregulation of the hormonal response to stress as well as the cardiovascular and other mood regulations that occur during acute stress. This is just another picture of showing that, for example, the regulation of the stress hormone protozal in -- among khat users to be flattened or blunted, meaning that the system has not behaved in a natural -- normal way in this drug using population.

So, more information about this program. The sites and achievements to date are included in our poster, which is manned by Dr. Motoher [spelled phonetically] and Akazeema [spelled phonetically]. Please stop by. It's poster number three. Finally, I'd like to thank my colleagues. I'd like to thank Dr. Kathy Michels as well as Dr. Mary Kautz [spelled phonetically] for their support -- but here's a list of all colleagues in Minnesota, Yemen, Europe, Africa, and a list of some of other consultants around the world who have been helping and facilitating and providing resources to our program. And this

is just a couple of pictures of some of our activities. Thank you for your attention.

Daofen Chen:
Thank you, Dr. Al'Absi. So we may have time for one or two questions. And such a diverse topic I wonder if speakers who have questions [unintelligible]. Any question from the audience? Yes, please?

Johansen Burns:
Thank you. Johansen Burns [spelled phonetically] from South Africa. I had a question about khat. In Southern Africa, cannabis is a source of income for many people, growing fields of cannabis and so on. I wonder if that was an issue -- you did mention, one of your slides, about it takes the place of other agricultural products. I was just wondering if there was a pressure from the community to keep growing khat because it may be a good livelihood, a source of that.

Mustafa Al'Absi:
Yes, indeed. Especially in East Africa, where it's a major source of income and foreign currency, like in Ethiopia, for example.

Daofen Chen:
Let's give another round of applause and thank our speakers. And let's move on to the next session.

II. MINI-SYMPOSIUM: GLOBAL VARIATIONS IN SUBSTANCE ABUSE

Woody Lin:
Good morning. The next session this morning is entitled "Global Variations in Substance Abuse." My name is Woody Lin, I'm a Program Officer in the National Institute on Drug Abuse. As the speaker presented in the last session, we learned that addiction is a chronic relaxing brain disease. According to our [unintelligible] addiction is one of the top 20 global health risks. And neither as a brain [unintelligible] in essence, that support research, training, education, and international collaborations on brain and behavior disorders associated with substance abuse.

Why's that? Because drug abuse have big impact on global society that cost life, it cost society, and it contribute to many disease, especially [unintelligible] disease. So, in terms of addressing addiction, finding solutions together really is the key. For that, we bring a panel of three speakers and some

other collaborators to this meeting and they will share their experience with us.

With that, our first speaker is Dr. Balachova.

Preventing FAS/ARND in Russian Children

Tatiana Balachova:
Thank you for your attention and it's a pleasure to be here. What I'm going to present has been done by a large group of international collaborators from U.S. and Russia and it is my pleasure to introduce Dr. Warice Esetcol [spelled phonetically] from San Francisco State University, who is our major research collaborator.

I always begin my presentations about studies with a -- just saying that Russia's a beautiful country with wonderful people. Very rich and interesting culture. But these days actually everyone care about Russia because of Sochi Olympic Games. But also Russia has one of the highest level of alcohol consumption in the world. You can see it's right here. We don't know exact rates and prevalence of fetal alcohol syndrome in Russia, but few studies which have been conducted indicated very high prevalence level.

One of our research study participants said Russia's a -- [unintelligible] in Russia and this is our tragic [unintelligible]. Very little was known about affairs in Russia in 2003 when we developed our international collaboration between universities in U.S. and in Russia. And we conducted several studies at this time with first grant, brain disorders [unintelligible], which was formative research. We conducted focus groups. And in two years we conducted surveys with more than 900 participants.

We learned from the study very important things. And this guided us in all our 10 years of studies now in Russia. We developed educational materials and training for physicians and currently we just completed our one study, which was focused on -- randomized -- it was randomized clinical trial -- to test intervention to prevent fetal alcohol exposure in Russia children. As you can see on the slide, we -- in both groups, in control group and intervention group -- in both conditions, participants significantly decreased alcohol consumption. We decreased it by 60 percent at least in both conditions, and treatment group has more significant changes. And we welcome you to come to speak with us to poster number four.

I want to focus on research capacity and we -- foundation of our work was constant [unintelligible] between researchers. We conducted seminars, lectures, [unintelligible], and we learned what we needed to do from our Russian collaborators. We trained faculty and students and developed [unintelligible] research group, which is very active in researching Russia and it also includes several consultants, experts in field from U.S. and Russia.

We trained graduate students, and you can see several dissertations have been completed, including different pieces of our work, and we are very proud to say that continuing research in several research centers now in Russia where faculty were trained by our faculty. More than 100 presentations and more than 70 publications included peer-reviewed presentations. And in 2006 we developed a website to disseminate information to general public and to health professionals. And in 2005, I found one search result fetal alcohol syndrome in Russia language. And at this time, you can see thousands of research results in Russian language from this field.

In 2011, [unintelligible] Council for Prevention of Harm from Alcohol and FAS was established at the major Russian Institute in Public Health in Moscow, which was very important result to provide sustainability for this research. And this council now advocates for research for providing services and to gain attention from government to this program.

In its conclusion, collaboration has been very successful and productive. And we learned a lot and we really believe that as our first session said, our plenary speaker said today, so much of research assessment is very important and can guide us for many years of research. FAS is easily modifiable behavioral among Russian women who can reduce and -- willing to reduce drinking. And physicians can with very low cost develop this intervention -- implement intervention and deliver intervention to number of women in Russia.

We had significant incidents from physicians and support from international community. And this line of international cooperation has served as a model in Russia for international cooperation and prevention research.

We identified next steps and actually next step is one of our next session on implementation because we understand that result implementation and support for implementation, it’s very

difficult to implement and this shows that our results implemented well and have significant impact. We also identify few gaps, which we understand we need to -- we need to do additional research and we hope we will be able to do this.

We thank our [unintelligible] and we thank all participants for support and help. Thank you.

Varieties of Impulsivity in Opiate and Stimulant Users

Jasmin Vassileva:
Thank you. It's a real honor to be here today to present the program of research that we have developed together with colleagues in Bulgaria over the past ten years. Thanks to the Fogarty International Center, [unintelligible] and the Brain Disorders Program.

So the focus of our research in Bulgaria was -- of our addiction research in Bulgaria was on impulsivity. Implicated in virtually all kinds of addictive behaviors with regards to drug use, both as an antecedent risk factor as well as a consequence of chronic drug use. Impulsivity is a very multi-dimensional construct, which has a variety of different personality trait manifestations, psychiatric manifestations, and distinct mental cognitive manifestations.

So, we -- just one -- but why did we need to go to Bulgaria to study impulsivity among drug users? Aren't there enough users here? Well, yes there are. But a major problem of studying drug users in the United States and Western Europe are the extremely high rates of poly-substance use and dependence. Such that, for example, among our samples in Chicago, up to 75 to 80 percent of heroin users are co-dependent on other drugs, which makes it virtually impossible -- or really difficult -- to disassociate the effects of different types of drugs in neurocognitive function.

So this is one of the reasons why we went to Bulgaria because we had access to [unintelligible] users that allowed us to overcome this difficulty. And to give you the context of why Bulgaria in particular has perry [spelled phonetically] whereas Western Europe or North America doesn't, it all happened after the fall of communism. During communism, illicit drug use was practically -- it was very minimal in Bulgaria.

There was alcohol and tobacco, the two main drugs, but no drugs were allowed in or out of the country. With the fall of

communism and the opening of the borders, Bulgaria quickly became a key [unintelligible] country on the Balkan drug route from Afghanistan to Western Europe, through which a lot of the heroin that's being used in Western Europe passes.

So, very quickly, heroin addiction became a major public health problem in the country. And this indeed when we partnered with our colleagues there to address this significant public health problem. And we started our first 21-hour study in 2003. Since then, patterns of drug use have changes. We tested -- in the first study we tested 100 pure heroin users and investigated some of the effects of psychopathy and other variables. Then, as we were reaching the end of this first stage of our research, we realized that there was a very different drug addiction epidemic that was happening in Bulgaria. And that was of amphetamines, as in the meantime, Bulgaria had become one of the major production centers for a synthetic type of amphetamines in Europe. It's just that now it's one of the top five countries of amphetamines.

When the two groups of -- this group of users, however, was very different from the heroin users that we were testing in that they were not overlapping, they were similarly not using many other drugs, which provided a unique opportunity to compare these two rare populations of mono-substance dependent pure drug users that could inform our scientific questions and move the science forward.

More recently, since Bulgaria joined the European Union in 2007, there's been a resurgence -- there's been increased rates of poly-substance use, so things are changing. The point that I want to make is how local changing patterns of drug use in different parts of the world really inform and drive our global scientific questions. So, with that in mind, our goal in our study was to determine which dimensions of impulsivity are common across addictions and which are unique to two specific classes of drugs: opiate and stimulants.

We administered very comprehensive impulsivity battery with a number of neurocognitive personality psychiatric measures of impulsivity as well as other related constructs. We tested over 300 subjects in that. For the outcomes, we have a rotation of five posters outside that you're welcome to come and see and talk to me.

But, conducting the study there allowed us to determine that opiate and stimulant addictions are -- have -- are distinct.

They have unique neuro-behavioral and personality correlates, which challenges the unitary account of drug addiction, which is currently the prevailing account in this field. Had we not done the study in Bulgaria, we would not have been able to discover these important differences between these two types of drug users that would inform our research.

Since then, we've done a lot of training in two different institutions in Bulgaria. They are sharing dissertations, disseminations, and so on. But one of our most significant research capacity building accomplishments was the collaborations that we established, both between and within collaborations between scientists of Bulgaria and U.S., which have led to the next stage of the project. Given that unique sample of participants that we have with prior approval [unintelligible] we started collecting genetic material and the next stage is to look at that -- how the role of genetics in these two different types of substance [unintelligible].

So basically it all led to new questions and new applications. So thank you very much.

Neurobiology of Methamphetamine Abuse and HIV Infection in Thai Adults

Napapon Sailasuta:
Good morning, everybody. I'd like to thank Dr. Lin for his [unintelligible] from [unintelligible]. And Kathleen for the opportunity to present to you the very early result of our study.

This -- just to show you our team members. So our 21 -- the aim of our 21 study has two components. The first is the infrastructure building for the Chiang Mai University in Thailand in northern Thailand. And the second component is the neurobiology study of the methamphetamine users HIV-positive patients and comorbidities. But for this talk, I will concentrate on the neurobiology of the study.

So I'll give you a little bit of background on the methamphetamine users. Basically, there's a lot of data out here in study in United States that established that using -- heavy users of methamphetamines and HIV infection cause neuronal damage. And also, there's only two studies in the U.S. that study -- that has result of comorbidity of the two conditions. But, in Thailand, is nothing have been done. And we know that in Thailand methamphetamine -- using methamphetamine is not --

what the local calls is called "yaba," which translate into "madness drugs." It's basically -- when you take yaba, it make you -- the person go crazy. And yaba is a crystalline form of methamphetamines, but 20 percent to 30 percent of meth, and the other heavy component is the caffeine and some other inner substance as well.

So the aim -- so the goal, or the aim of our study is that we want to [unintelligible] extent of neuronal damage among -- in the Thai adolescents between age 18 and 30 years old, who live in the northern triangle of Thailand, especially in the city of Chiang Mai and the surrounding area.

We will use the MRI and single [unintelligible] proton MRS approaches to study this translation -- cross-sectional studies. So our study population is very, basically, very small. We have 15 HIV-positive with meth negative, 15 HIV-negative with meth positive. And to do a diagnose, it was 15 HIV and meth and, of course, a healthy control. These patients or subjects will be recruited from the [unintelligible] Psychiatric Hospital and [unintelligible] Hospitals and other local communities in and around the city of Chiang Mai. And healthy control, we will recruit it from a pool of normal subject from other clinical studies at the University of Chiang Mai.

So our protocol, basically very simple. We do proton MRI, we do a three-dimensional MP ray, two T1 ray [spelled phonetically] images for maformatry [spelled phonetically] or the brain volume calculations. And followed by a [unintelligible] proton MRIs with those four [unintelligible] locations. And, of course, we also do neuropsychological evaluation in the subject as well.

So for the proton MRS, since the -- we start the project in late July basically and from -- of last year, 2013 -- and we work on the protocol and we first got the protocol approval in late September. And we have done -- and followed the training of the staff to do neuropsych, to do MRI, scanning, processing. We do the first subject scan in late October. So this study's been like maybe about three months old only. So, so far we have scanned six male subject, two healthy control, and one HIV-positive subject.

So this is the proton MRS result. You can see I only show the result from the frontal white matter of the -- of the three subject cases. You can see the first plot, we show that [unintelligible] creatine ratio of the meth subject is reduced compared to the healthy control with significant P. And also,

myonositol [spelled phonetically] over creatine in the same area is elevated in the meth users.

So what this mean, even though we only have a few subject, but to me, this prove our protocol and our result that we do this -- we do this right. Because these are the result of the U.S. population also, that we -- they found reduce in [unintelligible]. That mean since [unintelligible] in a proton MRS is the biomarker of neuronal -- of neurons. So that mean that in the meth users, neuronal damage -- so loss of neurons -- occur. And also minositol, which is the biomarker for the greosis [spelled phonetically], so that shows that the greosis in the methamphetamine is very high -- it's very high, so -- got elevated minositol to creatine.

And, of course, we also do the neuropsychological testing of these subjects. And I only show you the sample -- the raw data of the sample -- the two-test battery. We do the full battery I show below there. Time gate and ET -- and all those. But I show only the result of the [unintelligible] interfering trials and the group pegboard for the non-determinant hand. Well, you can see that because we only have a few subjects for the stoop tests that a lot of variability in the meth subject, the red dot is the meth subject and the black dot is the normal, healthy control. But this show that we can do the neuropsychological testing in this subject, which is very different from the -- from the other studies that we can show that strup [spelled phonetically] interference -- there's a lot of variability, but I think that as we get more subject done, we will be able to show something a little bit different.

So, as I said, this is just the only preliminary data and we were hoping that the results from the study will drive us to be used -- the data will be used for preliminary data for our 21. And we were hoping that also the result will guide the country to an effective meth treatment.

And with that I thank you for your attention.

Woody Lin:
With that, let's give another round of -- oh, okay. We have time for one question. Any from the audience? Let me ask one. We talked about variation in addiction and drug abuse. I just wonder in terms of human subject protections from the panel, do you have any comments in terms of the way you are doing research in the States and [unintelligible] what has been done in the foreign sites?

Tatiana Balachova:
It's excellent question because we -- when we began studies in 2003, there had been some change in human subject protection by all the programs, but at the same time we learned that university and actually major universities in Russia didn't have at this time [unintelligible]. So we had to follow all U.S. procedures and we have very strong requirements which probably all the universities I know all collaborate as discussed through those meetings. It -- one important [unintelligible] was to develop and design procedures which will acceptable by U.S. standards. And at this time we helped and with help of our university or be in U.S., we helped and provided assistance to Russian universities so they established very similar procedures and [unintelligible] which has been helpful for us [unintelligible].

Jasmin Vassileva:
We had the same experience in Bulgaria. When we started in 2003, there was no IRB at the university hospital where we did it and there was -- you can't hear me? When we started in 2003, similarly, there was no IRB at the university hospital where we conducted our research, but NIH was already doing trainings there. He was Russia and former communist countries. So we got in contact with the Bulgarian [unintelligible] what's his name who trained our team and we established an IRB at the hospital and since then we followed the same procedures as IRB in the United States. We haven't had any [unintelligible].

Woody Lin:
At my university in Northern Thailand, we have been working with John Hopkins University on HIV [unintelligible] since 2003. So I will be actually getting used to both sensitive issue like HIV infection and also [unintelligible]. At the beginning we spend probably half a year for HIRB application with three IRBs from John Hopkins University, our university IRB, and then IRB of Municipal Public Health. Now we get used to the field study and clean study among HIV infection and transfused patient. But this is the first time that we add on the neurobiological study. So I think we learning on how IRB issues are changing with a little bit with the lap issue this time.

Tatiana Balachova:
One important results of our collaboration was the establishment in St. Petersburg City University [unintelligible] and I'm head of this committee and the chain was more important -- was important for us -- for members of our committee.

Woody Lin:
Thank you. With that, we'll conclude this session. Let's give another round of applause to our speakers and panel.

III. MINI-SYMPOSIUM: FRONTIERS IN IMPLEMENTATION SCIENCE: LESSONS LEARNED

Kathleen Michels:
So I'd like to welcome the next panel. And also to remind all the speakers to make sure to speak into the microphone so everyone in the back can hear. So -- Dallas Anderson from National Institute on Ageing, who is our next moderator for the session on "Frontiers in Implementation Science and Lessons Learned."

Dallas Anderson:
Thank you. Good morning. We have six speakers and an array of topics: scaling up services for people with psychosis in Nigeria; establishing dementia care research programs in Thailand and in China; creating a center for Hispanic-American research; developing research capacity for mental health interventions for youth in Haiti; and finally, implementing practices to address neurocysticercosis in Burkina Faso.

Our speakers are Alex Cohen, Hongtu Chen, Sue Levkoff, David Kevin Johnson, and Pere Eddy Eustache, and Helene Carabin. And I'll ask each speaker to come to the podium and turn and to introduce yourself. Thank you.

Scaling Up Services for People with Psychosis in Nigeria: A Pilot Study

Alexander Cohen:
I'm not going to use PowerPoint for a five-minute presentation. I'm Alex Cohen, I'm from the London School of Hygiene and Tropical Medicine and my colleague, Oye Garage [spelled phonetically] and I have been looking at methods to scale up services for psychosis in Abaden and Nigeria. And I'll quickly go over what we've learned.

The mental health system in Abaden is basically traditional and spiritual healers. There are vast barriers to any sort of biomedical care at University College hospital. Primary care is probably entirely incapable of taking on the care of people with psychosis, which all augers poorly for image gap -- of image gap problem, which has been developed by WHO. But in terms of

lessons, I've been thinking about -- what's really interesting to me about this project and what can I tell my students or talk to my students about at London School of Hygiene. And I've concluded that the issue of sustainability is really central and very important in the field of global mental health.

People talk about sustainability, "Oh, we shouldn't put in resources because we won't be able to continue them. Governments won't pick up the cost. We'll have to be funding them forever." I think basically this is an excuse or a rationale for not instituting the best care possible. And I am guided in this belief by my former colleague Paul Farmer, who believes that we need -- that poor people -- people in low-resource places deserve the best care possible. So in terms of Abaden, I think we need to invest in mobile psychiatric teams to support services within primary care and to cut down the barriers for access to university college hospital and the state hospital and we need to develop psycho-social interventions and psychiatric rehabilitation.

Without very significant investment and services for people with psychosis, we will be supplying window dressing that will only give them very inadequate and perhaps deleterious interventions. So, that's all I'm going to say. Thank you.

Dementia Care in Thailand: Infrastructure And Research Development

Hongtu Chen:
In year 2011, we got this -- our 21. It's a collaboration between Brigham Woman's Hospital in Boston and Thai National Health Foundation in Bangkok and the third organization is called Institute of Society and Health, using their royal tie Ministry of Public Health. There were three groups together and we discussed -- we spend a year meeting and talking with Thai -- they have an organization called Association for Auzamerus Disease International [spelled phonetically] -- to discuss what do we want to do. What is the issue there? And the assumption basically is that disease is kind of what many -- symptomology is similar across the world and the -- but the solution should be different, should be localized or should be tailored to their situation.

So we start to propose -- start come up with a proposal to do a ethnography study in the country. And the original proposal was to sample families and patients and caregivers in one province

out of two sites. Once is relatively social, economical better off, another is a more poor area.

And that was original story, beginning of the story. Then something happened. Later of that year, there was a big flooding. And the flooding affect many aspects of the country. Government closed, the city closed, people evacuated. Then that, later, two things: one is, I had to later on file a lost-cost extension and the other thing is that our collaborator got inspired by this idea, by this proposal, and submitted small grant to the [unintelligible] House and got another grant to [unintelligible]. So the project got expanded. Originally, it was one province and it become nine province, a national survey study.

A national survey study need more people to do this ethnography research, it's quite time consuming. So we recruited about 40 people across the nine sites and trained them. And the training was quite extensive but everybody chipping knowledge and the [unintelligible] we did about a five workshops and then people were -- these people were all recruited from nine province -- then they go to their own place and work with local people, start to go to visit the families. And I was invited to join some of their trips.

And the Ministry for Public Health have their system over places. So we get to go to a place, fly there, and then they will have a van waiting for me and for my team. Finally, we did about 200 family -- cases. And among them, about 100 are dementia cases -- Alzheimer's disease and vascular dementia.

So, in terms of lesson I learned is that first I realized that in Thailand there are three very powerful systems based on the experience of families. One is this government system. They have multiple layers all the way down -- administrative system. The second is the Buddhist system. Everywhere you can see a temple and the people -- Monks will walk to people family. And the third system is the healthcare system. The healthcare system is a very well -- a very powerful system. And they -- from central system until the sub-district, every village you can see a building of what they call a primary care clinic. Then they also organize the community health workers, a system that they have organized and nurtured for 30 years. It's a very well-established system.

So, people -- my collaborators and myself also, we believe that whatever you do, you want to improve dementia care even if care

mostly happen in a family should rely on this healthcare system. The second is [unintelligible] lots of human resources. Besides the committed health workers that I mentioned, there's another emerging organization is called Senior Club. Lots of retired people increasingly more, and they will get together. They become increasingly more organized, not only because lots of reformer leaders from different aspects -- sectors of society join the group, they also bring some funding. So that group is quite a big resource. And they will come to us, we have meeting with them. They will say, "We need your guidance. We have people and money, but we don't know what to do."

And then the experience of visiting family -- lots of times these health workers will come visit us -- it's obvious that they have -- they have a very limited knowledge experience with dementia care, so training is a necessary component. And then local government, we slowly realized that they start to receive increasingly more funding to address the needs for elderly people, but what do is that money allocated into that category? Most of our administrators don't know, so they also want this kind of support. And the last lesson is that the research capacity is really important mainly because the policy change, I think, of course, is effected by lots of political forces, but science is big persuasion.

So with all this, I think my conclusion is the same as what Gretchen said before. The one thing we cannot pick up anything. So that gave me -- made me reflect on what is role there and I -- - in thinking back -- I feel this probably has to do with the theme over the meeting. I think it's a -- we play as soft catalyst or bring some rigor of science, some tools, and this soft catalyst or leadership is conditional. If we -- the conditions already in the local area, we can help organize something and inspire something and then [unintelligible] make science into a persuasive voice in policy making. Thank you.

Chinese Dementia Care Research Center

Sue Levkoff:
Thank you very much. My name is Sue Levkoff and I'm very happy to be here. I'm a former Fogarty R21 recipient from 2009, actually, but I wanted to come here because it's so important to me having been funded by the Fogarty and this project that has enabled us to continue to do many other activities.

I want to tell a story, actually. It's a Fogarty story. I -- my co-presenter here, Qua-li Huang [spelled phonetically] from

the Peking University Institute of Mental Health, I met her in 2002 when she was a Fogarty Fellow with Byron Goode's International Health Mental Health Training award and I was designated to be her mentor. And she became interested in dementia caregiving, which was my area of research. And after she left, we continued to work together and she submitted an Alzheimer's grant that we worked on together and started to -- she was a psychiatrist, but was becoming interested in dementia caregiving through, I don't know, but we got her to be interested in dementia caregiving, and she saw how important it was in terms of doing the work that she was going to do ultimately back in Beijing.

As a result of that experience, we then collaborated on an R21, which we received in 2009 when I was still at the Department of Social Medicine, which is now the Department of Global Health and Social Medicine, which Ann Becker is the Deputy Chair, so it's a small world here. And Byron Goode [spelled phonetically] is sitting in the audience. Hongtu and I have worked together and he worked with us on this. So anyway, so, the story is a small story and it's -- it's a Fogarty story because -- so, so then we got the R21 and then Byron got another Icourta [spelled phonetically] -- a second-phase funding of his Icourta. So that Qua-li is continuing to work on the Icourta and I've been invited to be a trainers for his current trainees on the Icourta. So, it's a really -- the Fogarty has really proved hugely instrumental in training a few generations of researchers and I just wanted to say that and give our thanks for that.

And I also want to agree with Hongtu, my colleague before me, who said we really are a soft catalyst. We really provide the catalyst for the groups that we're working with to really get their own resources and to gain additional resources to do what they want to do and I think that that's a very important point that -- how do I? Thank you. So anyway, this -- I'm really going to talk about infrastructure development. We have a poster, poster 42 up there, for additional information. But this was the Dementia Care and Research Center, this was the focus of the grant. She -- Dr. Huang already had clinical care and people there for research and she wanted to focus on health, education and training, and research. So this was put into place and what we were able to do was help with a variety of activities through this Fogarty funding.

The first was community education, and as so many other people have talked about, stigma is a huge issue for so many of these brain disorders. Stigma related to dementia in China is very --

it was an issue to get people to come into the clinics to get diagnosed. So, one of the first aspects of what we engaged in was a series of community outreach sessions where people trained would go out into the community, discuss dementia, give screening tests, and really it caught on. People were very willing to be screened and come back in for more diagnostic protocols. So this was trying to answer the question of "How do we reduce stigma?" And the way we do that is we go into the community, and we're there, and we talk to people.

We were also involved in continuous medical education because to really -- to really training caregivers across nationally throughout China in terms of what dementia is -- not informal caregivers, I'm taking about professional caregivers. Doctors, nurses, people in clinics. About what dementia was and Hongtu and I were again invited to be a part of several training programs where people were coming in from all across China and we provided sessions on research training and dementia caregiver research whereas other people were talking about actually dementia clinical care.

In addition to that, through this funding and through other funding, Qua-li was able to develop a national network of psycho-geriatrics. And, basically, she has, I don't know how many sites now across the country, but she has gone out and trained clinicians, not just primary care -- nurses, doctors, and other people -- so that there is a national network. And at those national centers, they are collecting data for a research database that she maintains at the Peking University Institute of Mental Health. So this has really expanded. And she also has developed a network with an Alzheimer's disease, international Alzheimer's disease Chinese, again, which Hongtu and I were invited to go and speak at several years ago.

Here's just a picture of [unintelligible] lecture. One of the presentations on psycho-geriatrics at the local sites. And this is the database, and this is ongoing, so this, you know, there's clinical data, neuropsychological data, neuropsychiatric and behavioral. Now the caregiving related questionnaires that we -- we actually connected up with Woo-Han University [spelled phonetically], a colleague of mine at Duke University, Ba Woo [spelled phonetically], who I've worked with. We brought her into this project and we trained over maybe 30 people to do research to collect information -- time's up? Yeah, that's fine, this is it. This is it.

We trained people to go out into the community both in Beijing and Woo-Han and collected data on caregivers. We had two Harvard students that got their undergraduate thesis funded through our work and because they had sites in China to collect data and to spend their summers, they got money from Harvard University -- they got additional money from Harvard, because they already had a site and were funded through us to do that. And, again, I think they were global medicine and -- global health and social medicine, or maybe they were at Harvard University -- they were undergraduates, yeah. I think Arthur Plineman [spelled phonetically] was their mentor.

And also now I've moved down to the University of South Carolina and am continuing to work with these data and global health and social medicine, of which I'm very appreciative, and I have my students there who are using these data. I have several Chinese students and when I have posters of my presentations and these Chinese social work students come into my office and they say, "I want to go back to China and do work." And so I say, "Well, we have data you can work with." So, it's really -- it's continuing to spawn many multiple training opportunities for individuals here in this country.

And I did apply for an RO1 which was scored "not funded" to do a Tai-Chi intervention for caregiver dementia diades, which we're going to resubmit. Thank you very much and I'm so appreciative to the Fogarty and -- this is a wonderful community of researchers. Thank you.

Center for Hispanic American Research Methods

David Johnson:
Do I need to do? Okay. Good morning, my name's -- can you hear me? Good morning. My name's David Johnson. I'm a Clinical Neuropsychologist and I work at the University of Kansas. I am recently Fogarty R21 recipient.

This slide is a little misleading because the name of the grant and the thrust of it, scientifically, is about the epidemiology and development of Alzheimer's disease in Costa Rica and Central America. This is one part, the CHARM, the Center for Hispanic-American Research Methods. And the "edad," which means "age" in Spanish for those of you not familiar with the language, is bio-behavioral clinical collaboration between my university and the University of Costa Rica. And I want to certainly give my most sincere thanks to the Fogarty for awarding this grant and it's certainly been pivotal in shaping mine and many other's

viewpoints about how we deliver care and apply preventative medicine in not only Costa Rica and Central America, but throughout Kansas and the United States.

CHARM is, effectively, something that I anticipated would be a grant product, some eventual outcome of this R21, however, as soon as we go in-country and started our pilot testing, it became painfully aware that it is something that I needed to put -- don't put the cart before the horse, if you will. It's just one piece of a more extensive collaboration to promote and develop health sciences at the University of Costa Rica by the KU biomedical initiative and behavioral research and would extend our behavioral research globally. Excuse me.

By result -- our program, the edad program, and CHARM by close proximity, has benefited from over $70,000 in start-up moneies from the university to initiate this health sciences initiatives in Costa Rica in which I've been eternally indebted for those start-up funds. So we've been working in Costa Rica for over five years just on the good graces of the university and now we're able to really, greatly, expand our reach and the scope of our project thanks to the Fogarty. And just, briefly, you know the University of Costa Rica and KU have enjoyed over 120 years of collaboration. We have strong university connections that actually date back to the Chicago World's Fair, where the chancellors of the two universities first met. And we share 30 academic programs, have trained over 1,000 exchange students, mostly undergraduates, and have a traditional built in mutualism that I'm actually very proud to participate in.

CHARM is also a direct extension of the type of assessment that I conduct as Director of Neuropsychology at the KU Alzheimer's Disease Center. And, again, I'm very thankful to the National Institutes of Ageing for making us the most recent Alzheimer 's disease center in the country and supporting us with the program project. But as a thematic focus of the center, we are trying to be leaders in the United States for the study of exercise and metabolism on brain health and the lifestyles that prevent Alzheimer's disease. And you can see we're rafted upon several RO1s that have given me great opportunity to extend the same types of quality research hypotheses into what we're doing in Costa Rica.

So the CHARM is actually using assessment tools and protocols that we've developed at the center and we actually house that data in a centralized database that's in -- that's managed by

the Department of Biostatistics in our Center for Research Methods and Data Analysis. And I'll tell you about that a little bit more.

And I want to just -- prevention of Alzheimer's disease strikes many people as a little bit odd, because isn't this a terrible, wasting disease that is without true treatment? But I also want to point out that I've spent most of my career working in the field of early diagnosis and have come recently to really appreciate that as we get better with early diagnosis and in appreciation of a pro-dremel [spelled phonetically] syndrome in Alzheimer's disease, and we don't have anything but symptomatic treatment at this time, that it becomes an imperative, national and globally, to really develop the prevention research surrounding Alzheimer's disease. And, of course, as cornerstones of that research is diet, exercise, adherence sciences, and development of good assessment tools so that we can screen early.

So EDAD's scientific aim is to examine the mortality advantage that we find in Costa Rica epidemiological data that indicates that lifestyle and environmental factors protect lower- and middle-income rural population sectors against age-related neurocognitive and physical declines. And, of course, our strong hypothesis that these lifestyle factors afford greater cardiovascular health, which in turn is the protective factor for healthy brain ageing.

And so the R21 really focuses on the cognitive determinance of physical fitness and functional ability in healthy [unintelligible] Costa Rican older adults. And so, I come to -- to pass and think about my first lesson that I wanted to share with you that I learned in this, which is getting this R21 in particular and linking it to the mission of Alzheimer's disease center to this particular project has resulted in a halo effect that's translated into much more university support. All of a sudden, I find myself being able to legitimately give Chairs and Deans talking points. And of the $70,000 that we received, we actually have received $30,000 of it since June when we were first funded.

I'll just close very briefly on the phases of the clinical research that we're conducting. There's several phases, phase one I've talked about where we've been training in-country our faculty at the UCR. We've developed a very large clinical research database based on my lab and my work at the Alzheimer's Disease Center. And I'm happy to point out that this is poster

34, and if anyone would like to talk more, we've established a public-private partnership with a research support company called Collectica and we're using something called the Data Documentation Initiative to support this idea of a clinical research data lifecycle. And we're able to really -- library and support in multiple languages across multiple projects. Now a library of about 450 clinical instruments and they're available to be served up either electronically if that's a medium your patient population is comfortable with or, in my case, optical character recognition and paper forms, which then get scanned in and brought into the database.

So it's been a great ride. It's been an eye-opening experience. And I have to, again, say that working in Costa Rica with colleagues like Monica Salazar has been extremely rewarding. And thank you.

Health Interventions for Youth in Haiti

Pere Eddy Eustache:
Good morning. My name is Father Eddy Eustache, and usually I'm called Pere. I'm here on the behalf of the whole team, [unintelligible] who has been involved in this project where we tried to [unintelligible] up our research capacity for mental health [unintelligible] in Haiti. I just want to -- I just want to address some big thank you to Kathy Michel for great support. She went to Haiti and showed us how important the support from Fogarty International has been to us.

What I will be presenting there context and the activities we led in this project. Dr. Ann Becker will provide -- will share with you -- their findings around this project. This research project is rooted in the context of the past earthquake in Haiti. Among the topics of discussion about the heavy burden of mental health in Haiti, because of the young people -- the youth has been left aside. When Dr. Becker went to Haiti, we got an opportunity to discuss about what could be done. And I raise -- I raised with the cause of the youth. And [unintelligible] her experience with the Fiji people, we decided to move forward to a great adventure in this project.

What we consider as to how we can first try to raise -- to raise awareness and as well motivation about this research culture. And we try first to evaluate the burden of mental health problem in the school and the second we try to -- to deliver that [unintelligible] training for -- about epidemiology social science and the research culture I talk about and to address

mental health disorders in Haiti. And as activity, we develop and implemented and -- a school-based pilot mental health project where we motivated students, parents, teachers, who became [unintelligible] around the process for the youth -- the [unintelligible] we providing -- [unintelligible] about that.

Anne Becker:
Thank you, Pere Eddy. And I'll just run through -- Pere Eddy just detailed the phases of our research study, which we're just winding up now -- we're just analyzing data now, so the findings we want to show are very preliminary, but we want to emphasize that if it seems like this study has a lot of moving parts, it really does, and that was intentional, it was intended to create a platform for research capacity building and collaborative research capacity building between our two institutions. So we wanted to include mixed methods, qualitative methods, focus group discussions, survey-based data, prevalence estimates, et cetera.

So here you see we have a picture of our initial didactic training session. We had about 33 trainees, including from the Ministry of Education, but mostly healthcare providers. We then created -- we had focus group discussions with the community teachers, youth, parents separately and created this training manual, which we would be happy to share with you, along with our findings on poster five later on today. And from there we went to a two-and-a-half day teacher training, which I think we have a picture of, which was successful and we'll share our measured results from that and the team, then, went forward to implement the program, which was to screen -- to conduct a school-based screening for Haitian secondary schools, for PTSD, major depression, and other serious psychological symptoms.

And then, after that, make a clinical referral, which was really part of the clinical team's responsibility, that was not part of our research, but then assign the student -- all students, whether or not they had need for clinical referral, to a teacher who'd been trained to help them navigate the healthcare system should they wish to pursue the referral. If they didn't have a referral, that was fine. They could talk to the teacher about homework, about resilience building, et cetera, et cetera.

So just a quick peek at who participated in our study. We had 22 secondary school teachers in Haiti's central plateau. These teachers were nominated by their principals. They were -- it was really a purpose of sample for people who were highly motivated to learn about mental health care delivery. And then

of the students, the students came from the same four schools. They were randomly selected and you see that there's a preponderance of males, which certainly reflects the demographic in the schools.

I should point out that the mean age is older than you might expect for school. That's because many Haitian students enter school late in the rural areas. So we actually, for a variety of reasons, partly because mental health policy lags behind what we'd like to see, we moved this so the minimum was 18 for our study. And you'll see, also, here there are a lot of data-- it's a busy slide -- but the upshot here, the headline, is that care access in this region, even though it's only [unintelligible] had been providing care in this region for over 25 years and care was free. There was very -- there's relatively low care access and many social-structural barriers, such as trans -- cost of transportation and affordability of medications that students mentioned.

So we want to share, again, some preliminary data. We -- after the teacher training, which was, again, a two-and-a-half day training, it was really simple. It was based on this curriculum, which was -- it was didactic and case-based. And we saw after -- you know, between pre-test and post-test we saw significant gain in knowledge about mental health. I don't have the data here, you can look at our poster if you're interested. We also saw a significant improvement in attitudes about mental healthcare delivery and the possibility of benefits of treatment from mental health. And, as you'll see here in this slide, the gains and knowledge and attitudes were sustained over the course of the intervention, which was approximately six weeks, so we were really happy to see -- you know, of course, we need to know would the knowledge be sustained further. But we're happy with what we have so far.

The headline here is that the burden of mental illness was high in this community.

You see here that if -- these are just the SCID content-based interview data, and if you see in the orange, we've applied very strict DSM-IV criteria, and the point prevalence of major depression was 11 percent. PTSD was 14 percent. You might argue that's lower than you'd expect by comparison, young adults from the community sample in the U.S., probably would have a PTSD 12-month prevalence of about three and a half percent. So this is high, maybe one would have expected higher, but you see here in the blue, we had many respondents who actually had sub-

clinical symptomatology that were judged to be still clinically worrisome. So, very high burden of mental illness just screening for these two disorders. In terms of feasibility of our teacher-student pairing, we found that students were able -- the majority of students and teachers were able to meet, and when they did meet, 75 percent of them did address treatment or adherence to treatment in that meeting. So we could -- we weren't sure about the local acceptability of this mechanism of task-sharing to teachers to be navigators, and this is our initial proof of concept. And overall if you see in the green and the blue, the bright blue bars, the students and teachers who did meet overwhelming thought this was a very positive experience. And I want to hand the microphone back to Pere Eddy to talk about lessons learned.

Pere Eddy Eustache:
The first lesson that we learned, it was how to take into account the needs, the huge needs in the people, and when we found out how enthusiastic people were about embracing this new project, it helped us understand that presenting something that they really need was a major pathway to follow to get to the success today. Anne, any further?

Anne Becker:
The other challenge that we thought we overcame really well was, initially communication was very complicated by the fact that Internet service, Internet access in the region we were working in wasn't always very good, neither was phone access. We actually worked rather iteratively in terms of bringing the Haiti-based team to Boston and vice versa, the Boston-based team went to Haiti, especially during data collection where one of our team members from Boston went every week to accompany the team in Haiti who were really collecting the data, but we were there as an extra pair of hands.

Pere Eddy Eustache:
The team tended sometimes to feel discouraged, but as long as we are progressing in the process, they found that what they were doing was so useful that they become more and more encouraged, and they kept going with the project, who led us today where we are.

Anne Becker:
Yes, this is our last slide, and really this is a thank you slide, as you can see. I don't think we even have all the names of the members of Iquipwaso [spelled phonetically] on slide but

we want to acknowledge them, and also our tremendous thanks to Fogarty and the National Institute of Mental Health. Thank you.

[applause]

Implementing Practices to Address Neurocysticercosis in Burkina Faso

Helene Carabin:
Hi. So my name is Helene Carabin. I'm here with my colleague Athanase Millogo, and we're -- I'm an infectious disease epidemiologist, and Athanase is a pediatric neurologist working in Bobo-Dioulasso in Burkina Faso. So today what we would like to talk to you about is a little bit how we use participatory community research in the form of preceed-proceed approach, in order to implement an intervention in one of the poorest countries of the world. So I'll talk to you a little bit of where we came from and where we ended up, and then we'll go through a few barriers that we faced, and Athanase will specifically talk of the barriers that he faces as a researcher in one of those very poor countries, and then we'll talk a little bit about the lessons learned, the solutions that we found to that. So not many results, these are in the poster, we just wanted more to talk to you about what happened.

So when we started this study, which is funded by the Fortune and INDS, in the R21 we went through three villages and confirmed that neurocysticercosis, which is a parasitic disease caused by Taenia solium, was very prevalent in villages where pigs were being raised. In fact, in the two villages where pigs were raised, 45 percent of people with epilepsy had lesions of neurocysticercosis in their brain, whereas the one village that didn't raise pigs had none. And we did not make up the data, it was real data. So we thought, "Okay, great, we found this, so we're going to try and control epilepsy, we're going to try and prevent epilepsy through an intervention by improving pig production," because this is a zoonotic disease transmitted between humans and pigs. So there had been an experience in Tanzania that improving pig production could really help. So in order to do this, we first started with a focus group and in-depth interview with people in pilot villages in the three provinces where we wanted to work, and asked them, "Well, what do you think about improving pig management? What do you think about keeping your pigs in pens and feeding them?" But also we asked them, "Okay, what do you feel about sanitation, using latrines?" And we asked questions about epilepsy as well. And these focus group discussions, what came out of them was, "Oh,

we would love to keep our pigs in pens, but we can barely feed ourselves, especially during the dry season, so you cannot ask us to feed the pigs, whereas if we let them roam they can find their own food." And very often when there's a really big drought and there's nothing to eat, they'll just kill the pig and eat it. So the pen idea was just not feasible in such a dry, poor environment.

Therefore, we switched gears, because when we started asking questions about latrines, we found out that first, there was no major cultural barrier to using latrines, unlike what's seen in Benin. In Benin, they believe that if they go use a latrine, when their stool goes in the hole, it's part of themselves that disappears. We didn't have that in Burkina. And people were very aware that open-air defecation was a bad thing. Therefore, we thought, "Okay, we are going to try and find a sustainable, cheap approach to control this." So we looked at the literature and learned about community-led total sanitation, CLTS, that had been used all over the world, it's participatory in the community, but it takes, like, a month or two to implement. So we got in touch with WaterAid, who's in charge of implementing that in Burkina Faso, but [laughs] they were asking us, like, for $500,000 to help us do this, whereas this was their job [laughs] to do it for the government, and there was just no way we managed to negotiate with them to do this, because we were bringing an evaluation of the effectiveness of this approach, but they just would not buy it.

So again we had to switch gears. So we went to Water and Sanitation for Africa, and they were actually really helpful. And they're the one who told us, "Listen, CLTS, although the government has decided that this was the way to go, they don't have the money for it because it's too long." You have to stay so long in each village that it's not realistic. Therefore we went for another approach, which was called PHAST, it's very similar to CLTS, but it's shorter, and it's an approach that has been developed with WHO. And what it does, is people go to the village and they discuss about sanitation, and we adapted the usual PHAST, which is participatory hygiene sanitation transformation; we adapted it to cysticercosis. We also put in the picture the pigs, and the pigs eating human feces, and how we can prevent that, and how we should wash the food and cook the meat and all of that.

So -- and then the other thing that we did, so whereas WaterAid were asking us for humongous amounts of money to help with implementation of CLTS, we talked to a movie producer who had

multiple international awards. Sawadogo is his name. And he said, "You know what, I will do a movie about this to educate people on cysticercosis, its transmission, and how to prevent neurocysticercosis and epilepsy caused by cysticercosis." So, at first we wanted to have a 15-minute movie. The guy ended up giving us a 52-minute movie, and it's a comedy about cysticercosis, but it also talks about stigmatization of epilepsy, talks how epilepsy is preventable, and also talks about washing your food before eating it and not defecating outside. So after each session of the movie, of course, they discussed the major lessons. So the goal, our goal is to maximize sustainability, to develop something that's not super expensive and that the government can move on with once we're gone.

So a few of the things, the barriers that we really faced in working in this setting, is people are extremely poor. We're working in three really rural areas. Some years when there's a drought, really they barely can eat, it's extremely, extremely poor. So I'm working on another project in China where we're using social marketing of latrine building. But there in Burkina that's not really feasible because even the concept of investing in something is really hard to work with because there's so few resources. So we really have to focus on sustainable solutions that are probably less sexy, and are not going to be immediately effective. It's less right in your face like a big treatment, or vaccinating pigs, but they're more likely to be sustainable.

Another thing we saw is that whenever we mentioned the word "research," people think that we come with a huge amount of money. And that's a consequence, unfortunately, of some of the really, really big funding agencies, such as Gates Foundation or USAID, or these people that come with a lot, a lot, a lot of money, that they think that any researcher will come with so much money that the people we work with, and even the field workers, expect that we have infinite resources [laughs], so that's been difficult. And then working, again, with the people in the field is that research participation is not a priority for them, they have to try to find food.

Another bear we've been facing lately is that there's been a development of mining activities. So we're doing a follow-up study, but people are leaving, because they're moving to the mines. So, anyway, that will bring me a lot of epidemiological, methodological challenges, which are going to be fun to deal with, but we've had to really adapt to this. And communication

has been an issue, but we've, you know, we use the phone [laughs] when it doesn't work, and we just managed to talk. It's been more challenging with some other of our colleagues, but we've managed to figure it out. So now Athanase is going to talk about his own barriers.

Athanase Millogo:
Thank you, Helene. Thank you, Kathy, for my invitation. We -- in such a setting, we faced barriers. Researchers working in this condition are -- really is challenging. First, researchers, policy makers, and population have different priorities for the population. They have to face the daily needs, what is not so evident for the policy makers. There are a lot of images, endemic, chronic, stigmatized for this part, and this is for the researchers, the problem is to face endemic, chronic, and stigmatized affections, whereas for the policy makers, they need to face public health emergencies, such as TB, such as malaria or HIV infection, which rate is pretty high in my country right now. The second side is the importance of quality of research in this kind of setting. When in this setting, when the word "project" is pronounced, people think that we have a lot of money to share, and because of that, many times we had to pay for them, for their own needs. For example, for malaria, for diarrhea, if we are in the village working on our project, if someone becomes sick, they just come to us and, "Provide money, because we know that you may be very rich, you have to pay for because you are working in our village." So, and furthermore, there's no academic institutional support. Our front for this research was administrated by an NGO in Bobo-Dioulasso, which costs part of our budget since [unintelligible] couldn't perform at the university level. So they were to perform in the private structure. And in the same time, there was no minimal standard for analysis of our [unintelligible] at the university level. And also at the university level, there was no capacity building infrastructure, so we cannot plan to -- thank you. It is time. But for me, it is like our body is still in the Middle Age and our spirits in the 21st century, what is very frustrating and what is a very good challenge for us in this kind of setting. Thank you. Helene.

Helene Carabin:
So I will really very, very briefly just talk about the lessons learned. First of all, we worked very closely together. I think you all know that.

So, yes, so, yes, I am going to leave it at that. But I just do have -- this is in our posters, just first results of the

distribution of porcine and human cysticercosis. Just come to the poster. And I do have to take the time to mention Dr. Linda Cowan, who really helped me out with the R21 initially. I came in there as an epidemiologist; I knew nothing about epilepsy. And she died on December 31. Thank you.

[applause]

Dallas Anderson:
Well, we only have just a few minutes, couple minutes for questions. Do we have any questions from the audience?

Male Speaker:
So we've heard a couple of talks on epilepsy, and in Uganda, there appears to be a frightening incidence of childhood epilepsy that's so high I actually don't quote the numbers because no one would take them seriously, and so I tone down the things when I try to publish a paper or produce a report, and whenever I speak to someone about the origin, they shrug their shoulders, these are good local neurologists, the few of them that are out there, and they say, "Well, maybe malaria." And we've also talked about -- so a consequence of cerebral malaria, we all understand, is epilepsy, but there's a lot of other febrile illnesses that affect the brain in that part of the world. We don't see very much neurocysticercosis in Uganda, but I also recognize that my sample selection for the images that we do get, for other children, may be very biased. So I'm interested in getting the causes. How many major causes do we think there are of epilepsy in sub-Saharan Africa? How well do we even know the incidents, and what do we do as a community to try and set up the science needed to address them in some kind of meaningful priority? I'm really interested in your thoughts, because I don't know the answers to any of those questions.

Helene Carabin:
So neurocysticercosis-associated epilepsy tends to be -- the onset is often in young adulthood, so it's possible you don't see that in really younger children. It does happen, but it may not be as common. Now, the other causes of epilepsy, I think Athanase is more likely to help you with this, but epilepsy, you know, as Gretchen will tell you, is very, very hard to study because it's so stigmatized. So even if you have a screening questionnaire, some people may not answer your questions honestly, although you tried to use the ILEA-recognized questionnaire, you're going to miss some cases, and it's just very difficult, but it's by trying to reduce the stigmatization

around epilepsy that I think we'll get to better estimates. So I think that's why Gretchen's doing is so important. Yeah?

[inaudible commentary]

Angelina Kakooza:
Thank you very much for your presentation. My name is Angelina Kakooza from the school of medicine, Makerere University College of Health Sciences. In response to the question of the previous person, who asked about epilepsy in Uganda, we did a multi-site study, the SEEDS study on epilepsy in Africa, and Uganda was one of the sites. I was the PI for the Iganga demographic surveillance site, and we found a high incidence of febrile convulsions as one of the risk factors for these children who developed epilepsy, as well as parasitic infestations. The publication is in process, and I hope then you'll be able to see more of the risk factors that we found. Thank you.

Male Speaker:
On that note of Angelina, we actually set up a kind of large animal trial looking at cerebral malaria in mice to try to look at adjunctive therapy, because rather strikingly, from listening to Angelina in the past, it wasn't apparent that we could find any animal model to teach us the mechanisms we need to institute, to better treat the children with cerebral malaria and cut down what seems like an almost incredible incidence of childhood malaria in that part of the world, and I presume this applies to all malaria-prone regions of the world. And we got one of them epilepsy foundations to back this, it's expensive to do, but I'd very much like to hear Angelina's thoughts on how we develop the science needed to begin to address what seems to be one, and additional causes for which we don't have mechanisms. In other words, we don't have the mechanism knowing how to better treat these illnesses to cut down what seems a well-established post-infectious incidence, which seems way too high for where our science is.

Dallas Anderson:
Well, we need to wrap it up. So let's thank the panel for their contributions today.

[applause]

Female Speaker:
Thank you, everybody. So we'll go to break now, and please be back by 11:10.

IV. MINI-SYMPOSIUM: INFECTIOUS DISEASES

Jeymohan Joseph:
So welcome to the mini-symposium on infectious diseases. My name is Jeymohan Joseph. I'm with the HIV, neuropathogenesis and therapeutics branch at NIMH. So this session will be really broken up into two components. The first two talks will focus on CNS effects of malaria and African trypanosomiasis. The second component will cover HIV-associated neurologic complications in adult and pediatric populations. So our discussion section will cover both topic areas, but just for convenience we have these two components. And before we go into the HIV piece, I'll give a brief overview of the NeuroAIDS program. But first, we'll start with our keynote speech with Drs. Chandy and Idro. Welcome.

Chandy John:
So I would like to thank Fogarty for allowing us to give this talk, and I have two introductory remarks. The first is that this is very much a collaborative group, we've been really fortunate to have a great group of individuals to work with, so, though Richard and I are giving this talk, it is the work of ourselves, Bob Opoka, Paul Bangirana, and Mike Boivin, all of whom are here at this session. The second is that we've also been fortunate in having three fantastic program officials. Kathy Michels, who we all know and love, has been with us from the beginning, 10 years and counting. Deborah Hirtz with NINDS joined us for the R01, and then Barbara Sina is our is our program officer for the D43 we got for the infectious diseases training grad. And these program officers have been insightful, they've been supportive, and they've been deeply committed to the work. And so, at this point, I will answer the question that all of you are asking, which is, "Why is he wearing that hat?"

[laughter]

The reason I'm wearing that hat is to do this. Hats off to you, Kathy, Deborah, and Barbara. Thank you. Okay, moving on. My prop is here; I will move on to the science. So I'm just going to go through -- we have 15 minutes, and we want to cover capacity building as well, so I'm just going to go through quite quickly some of the research findings from these studies. The studies originated because we wanted to ask whether cerebral malaria was associated with cognitive impairment. We had a nice setup for that in some of the discussion at the end of the last set of talks, and interestingly, at the time we started this

study back in 2003, there had been several retrospective studies looking at cerebral malaria and cognitive impairment, including some by Michael Boivin, but no prospective studies.

So Michael came to me with the idea of looking at cognitive impairment in cerebral malaria, and we talked to Richard and Bob about this, and eventually this study began, and the results of the first study, the R21 study, was that we did find prospectively that cerebral malaria was associated with cognitive impairment. The study design was that children with cerebral malaria were enrolled as well as children with uncomplicated malaria, and community children who were from the same extended family or neighborhood of the children with cerebral malaria, so presumably similar in other factors, like socioeconomic status, that could affect cognition. And what we found, summarized in this abstract that was published in Pediatrics, was that six months after discharge, about 21 percent of children with cerebral malaria had cognition impairment, as compared to about six percent of our community controls.

So a striking difference, and when we adjust it for a number of other factors that are associated with cognitive impairment, there was a 3.7-fold increase in the risk of the cognitive impairment at six months. Well, this was good as far as it went. We got a little bit of flak because people said we couldn't say that children with cerebral malaria had long-term cognitive impairment if we were only looking at six months. So we did that study. We looked at children two years later. This is an example of how an initial study can lead to other things, so we were applying for the R01, we were sort of between funding. Kathy managed to get us some bridge funding.

The University of Minnesota kicked in some funding, and we did a study looking at these same children at two years, and what we found was essentially the same thing, and that was about 26 percent of them had cognitive impairment as compared to about eight percent of the controls, and the fold increase in the risk of cognitive impairment was essentially identical, 3.7-fold. So fairly definitive studies showing an association, we couldn't show Kosation, but an association between cerebral malaria and cognitive impairment long-term.

We were disappointed to find that there were not a lot of clinical factors that were associated with an increased risk of cognitive impairment after cerebral malaria, because we were trying to think of predictors so we could intervene. But number

of seizures in the hospital was associated with impairment at six months, and the presence of hyperreflexia exam or neurologic deficit at three months were associated with cognitive impairment at two years.

My background is in pediatric infectious diseases and immunology, and so I wanted to look at how the host response might affect cognitive outcomes. We know that the host response is very important in severity of disease in malaria and probably plays a major role in whether kids get cerebral malaria or uncomplicated malaria. And so we looked at a number of pro- and anti-inflammatory factors and published several papers on this, but I'm just going to highlight one of the more interesting findings. We looked a suite of 10 pro- and anti-inflammatory cytokines that had been seen in severe malaria in other studies, and looked at whether these were associated with cognitive impairment in cerebral malaria. And what we found was that only one cytokine was associated with cognitive impairment, and that cytokine was TNF, and it was only TNF in the cerebral spinal fluid, so it was local TNF production, and it was associated with worse working memory scores and worse attention at six months. So this was very interesting because there were animal studies that suggested the same thing. As has been mentioned, animal models of cerebral malaria are imperfect because you can't use P. falciparum, but these animal models had suggested the same thing, and this suggested a potential area for intervention in trying to decrease production of TNF.

Michael reviewed a study that he, Paul, and others did on computerized cognitive rehabilitation therapy in children who had cerebral malaria. From my perspective, I was trying to understand how the host response affects the risk of cognitive impairment so we could think about interventions at the time of disease that would decrease or prevent cognitive impairment. But obviously, there are hundreds of thousands of children who have had cerebral malaria, and who now have a risk of or do have cognitive impairment, so the question was, could anything be done about these children? And so Michael and Paul did this study looking at computerized cognitive rehabilitation therapy and were able to show that there were immediate neuropsychological and behavioral benefits from doing CCRT. And so the follow-up to that study is the R01 they now have looking at whether CCRT is useful long-term for children with severe malaria.

The R01 that followed from the R21 then asked the question of, what happens to children who are younger with cerebral malaria?

The first study looked at the kids from five to 12; this study looked at children from 18 months to five years, which is a much more common period to develop cerebral malaria in Kampala. We now had the technical tools to study children at younger ages. So for cognitive ability, we used the Mullen and adapted it to the Ugandan situation, and for attention and associative memory, we used two tools that have been developed at the University of Minnesota by Elsa Shapiro and Steve Hughes, the ECBT test and the color-object association test, adapted them to the Ugandan context, and were able to get very reproducible and reliable results in young children. And let me see if -- yeah.

So, just walking you through these slides, the top line here is community children; the green line is children with severe malarial anemia, so another form of severe malaria that's far more common than cerebral malaria, almost 10 times as common. It's estimated that anywhere from one and a half million to 5 million children every year have severe malarial anemia. And the bottom line is the children with cerebral malaria. And so the question here was, is cognitive impairment seen in younger children with cerebral malaria, and is it seen in forms of severe malaria that don't overtly affect the central nervous system, because severe malarial anemia has a very low mortality of transfused, and they have no CNS signs except perhaps the occasional seizure. And these children actually didn't have seizures; we screened out children who had had seizures. So the mortality in our SMA group was very low; only one child of 224 that we enrolled died, whereas mortality in CM is about 13 percent, so big difference in mortality. But what was striking was that for overall cognitive ability by the Mullen, we saw significantly lower scores in both kids with SMA and kids with cerebral malaria, and these differences translate into a difference at 12 months of about 11 IQ points for SMA and 14 for CM. We also saw differences in attention that were close to significant for SMA, and were significant for cerebral malaria, but interestingly, did not see any difference in associative memory for SMA but a big difference for children with cerebral malaria.

So these results showed several things. One was that, yes, younger children are affected. The second was that, for overall cognitive ability, it looks like severe malarial anemia really is related to impaired overall cognitive ability, which has a huge public health implication because there are so many more of these children than there are children with cerebral malaria. And it also suggested that the areas that are affected are different, because we didn't see any effect in associate memory

with kids with SMA, whereas we saw a striking effect in the children with cerebral malaria. So we're now trying to look at the pathways by which this may occur. So our new Fogarty studies are the computerized cognitive rehab study that Michael is running, and then a grant we just received to look at neurodevelopmental outcomes in the five most common forms of severe malaria, trying to ask the question, is cognitive impairment something that occurs in all forms of severe malaria, or is it restricted to the two we found? Because if it occurs across severe malaria, then we need to think about interventions for a much larger group of children. The other question is whether it affects the same areas in the other forms of severe malaria, so we're doing the same types of cognitive tests to get a very, sort of fine-tuned assessment of which areas are being affected. And the third thing is what pathways are, so we're looking at genetic pathways, we're looking at inflammatory pathways, we're looking at endothelial activation, and we're looking at a number of other factors to really try and hone in on what's going on with these kids and why they have cognitive impairment.

Our studies have had a number of other findings. I just want to call your attention to poster 10 which Bob Opoka is presenting, which is about the risk of readmission to the hospital in children with severe malaria. We found that there's a strikingly increased risk of readmission, so this was sort of a side finding, and now we're trying to figure out what to do about that. So an example of how studies focused on one thing can give you very important information about another thing. But I'm going to turn the podium over to Richard Idro, because we've also done quite a few capacity-building initiatives, and Richard, Paul, and Bob have been at the center of these, so Richard's going to talk about those.

Cognitive and Neurologic Sequelae of Cerebral Malaria

Richard Idro:
Thank you, Chandy. The second part of -- the second aim of our initial R21 was really to build capacity within the university and the teaching hospital where these studies were being conducted, and specifically we aimed to establish a center for cerebral malaria research, and the objective of this center was to help us train the research personnel in the conduct and management of clinical studies, and to provide an environment conducive for the conduct of clinical research. We have had quite a number of achievements through the implementation of

these studies, the first of which is research-specific training. And as -- right from the beginning we were able to develop a core curriculum which all our study personnel have undertaken, including the trainees who have passed through this system. And this included basic principles in the conduct of research, good clinical practice, the performing and obtaining informed consent, documentation, and basic statistics, including the use of different software in data management.

Secondly, we looked at -- we're dealing with a group of extremely sick children, so high-dependence care and improved care for the children we handle. Basics of immunology, neurology, and neuropsychology. And following this, we have now expanded into other areas of other infectious diseases, and we have established three new sites and actually are in the process of establishing a fourth, and we have literally become a center of excellence in neuropsychological assessment and child developmental assessment in the region thanks to Michael, Bruno [spelled phonetically], and Paul. Within the center we have improved our research environment, and one of the things with a different context has been establishment of an intensive care unit within Mulago Hospital. This is now a six-bed unit, which Bob, I, and two other colleagues ran with in the hospital, so we provide clinical care here and our patients are admitted through the center. We've been able to establish connectivity, provision of high-speed Internet within the departmental offices, but have also become a site for training, so we have students from several universities, especially Case Western Reserve Minnesota, Michigan State, and Michigan, who take off and have elective training in international health and research with us in our center.

Within the institution, the local institution, there's been quite an enormous capacity building. The initial R21 now led to three R01s, a U01, and one D43 grant. And just a few things about the D43 grant: we now have five Ph.D. students and three Master's of medicine students who are being supported, and we'd like to really appreciate and thank for this capacity building, and in the few years to come, these students will be available. In addition, this grant offered for us one post-doctoral position, which is in place. We started as junior investigators and three of us, we have since completed the doctoral training and post-doctoral training, and the three of us are now faculty at the university. Other than the R01 NIH funding, we have been able to obtain grants from other sources, the International AIDS Society, the Waterloo Foundation, the Lara Foundation, the Royal College of Medicine, so really a number of grants have followed

and the studies have expanded tremendously. Over the 10 years we have had at least 26 publications, and several submitted and along the way, and a lot of this work has now led to the first-ever published book on neuropsychology edited by Bruno and Michael.

Our research staff have also obtained advanced training. The first three medical officers, physicians, have all completed their residency training, and they are now pediatricians in different units working with either research or providing clinical care. Three of our initial neuropsychology assessors, are on commonwealth scholarships, and two of them have completed their Master's and the third is completing in the U.K. And three of our research administrators have also obtained graduate training and NIH-specific grant management. So really, in total, the initial grant has really expanded, and not only have we been able to achieve scientific excellence, but also a significant capacity in the institution. Thank you.

[applause]

Jeymohan Joseph:
We'll now hear from Dr. Marina on neural dysfunction and neuro-inflammation in African brain disorders.

Neural Dysfunction and Neuro-inflammation in African Brain Disorders

Marina Bentivoglio:
I'm actually reporting on an R21 grant, and the slot is five minutes, so I will be very brief, but I really would like to take the chance to thank Fogarty and Kathy Michels in particular, a really wonderful program officer, and we've had the privilege also to be in Africa many times together and a number of adventures.

So this is a consortium formed by Sweden, Italy, and Cameroon, the University of Yaoundé I, with the contribution of the Institut National de la Recherche Biomédicale in Kinshasa, Democratic Republic of Congo, where Jean-Jacques Muyembe and Dieudonné Mumba, who is in the audience, have been and are extremely helpful. The, I would say, byproduct during the project, we've also been working with a number of colleagues, actually, from limited resource countries, a book, “Neglected Tropical Diseases and Conditions of the Nervous System,” where many diseases dealt with in this symposium have dedicated chapters. It's 22 chapters and the conditions go from khat

addiction to dietary salt to venom bites, and so forth. So we hope that this is going to be a useful contribution to the neuroscience and neurology of neglected tropical diseases.

The project is about sleeping sickness, or Human African trypanosomiasis, HAT, which is really, it has been defined as the most neglected among neglected tropical diseases. I will be very brief. The Kosative agent is a parasite, Trypanosoma brucei, extracellular, and the number of cases, that was on the rise at the end of last century, is now declining. The vector is the Tsetse fly of the genus Glossina, so the disease is spread in sub-Saharan Africa in the Tsetse belt. And there is a worry right now that this disease could suffer from the punishment of success, due to, of course, the surveillance and control programs. The reservoir of the gambiense form of the disease, which is the most, the largest number of cases are actually humans, and through decades we have seen that whenever the control and surveillance of the cases decreases, then the disease bursts again with the lag actually of 10 years, and favored by political instability that unfortunately we can see now in many African countries.

Now, the disease is in two stages. First the peripheral invasion, through the blood and the lymph, and then the parasite crosses the blood-brain barrier, and there is an encephalitic stage, which is fatal if left untreated. The drugs to cure stage two diseases of both forms, I mentioned gambiense, and then the other form which is more acute is rhodesiense, and the only drug that can cure both forms of the disease is [unintelligible] the toxics is an arsenical compound that can be either lethal and the therapy is very painful and the patients refused it.

Now, there are no certain stage criteria that been proposed by WHO years ago and are under discussion based on the number white blood cells into the cerebrospinal fluid. Now, the project really, I think it was a big success, and it was for us, extremely stimulating to interact. It went from molecular and cell biology to the patient, so I will very quickly take you through. We have been studying and still there are studies going on. The mechanism of the multistep crossing of the parasite of the blood brain barrier, a biomarker chemical [unintelligible] involved in this process has been identified and those who they validated in patients, but cannot be the only biomarker. We need the biomarkers for disease severity and for monitoring the clinically, the patients.

Studies are going on on a number of mechanism which open perspective, also another neurological diseases and basic neuroscience in general, a bottle nitric oxide, which actually would be protective in this condition, because it would be the molecule that closes the door behind the parasites, and avoids continuing entering of the parasites. In animal models, we've been phenotyping the sleep disorder, because clinically it is very characteristic of sleeping sickness and from which disease derive its name, disorders of the sleep/wake cycle and of the internal structure of sleep. I don't have time to go into that, but this is a very important sign and symptom of the patients that is somehow a unique feature of the disease.

Together with Cameroonian [spelled phonetically] students, discourse their thesis on this topic. We've been monitoring, during the period of parasite invasion, the sleep and wake in rat, in infected rats. And we could detect a number of changes that had to be validated in humans, and we also could check something important from the translation point of view, that the sleep/wake changes were very nicely correlated with rest activity changes in the animal models. This brought us in the field to the use of very simple non-invasive device, which is the actograph, the gold standard for sleep studies is polysomnogrophy, but this of course, difficult applied in the source limited setting.

So, a pilot study is being performed during the R21 grant. I will not go into much detail, but you may see yourself, the night and day, the bars below the light and dark are night and day activity during the day of course. Less activity, sleep, during the night is a validated technique with very simple algorithm that can be applied, very user friendly, and Alfred Njamnshi is here, ready to answer all questions. The files can be sent by cell phone because they're very light, and you can see the disruption in a patient, and also, very important to monitor clinically infected children. You have here a five year old child compared to a healthy control. Here, you also have an image of ongoing automatic monitoring [unintelligible] again, helped by our colleagues in the Congo, still going on to validate further the data.

Now, big component of capacity building at University of Yaoundé 1, we have been seeing, actually, literally during the project, from a big hall, to a building, a neuroscience lab, the students, Cameroonian students have been trained in European labs. I have to say, the return home is not so easy. Not so much for the volunteers of the student, but because the

bureaucracy in some African countries, for the recruitments is very, very tough. And again, our African colleague can comment on that. The schools of residency neurology in Yaoundé is really blooming. There is a poster explaining our itinerary during the R021 and the capacity building and photos of a number of students, 41.

And with this I close, I have to say that due to an emergency created by the snow storm in United States and closing down of airports, I am very sorry, but I have to leave. And this is not very African, the snowstorm, but this unfortunately interfering with an African story, but Alfred Njamnshi is here for all the panel discussion. And many thanks, again, to all of you, and to Kathy in particular.

[applause]

Alfred Njamnshi:
So, thank you Marina. So, before we start on the talks focused on HIV neuro AIDS breakthrough from the brain disorders program, I wanted to give you a big picture overview of the success of neuro AIDS efforts under this initiative, and I am its scientific goals and priorities in the neuro AIDS area that's linked to this initiative.

So, NIMH has really partnered with Fogarty since 2003, since the beginning of this program, and we've been, we have funded close to 16 grants, some of them with our sister institutes, NINDS, 16 grants in this area of neuro AIDS. And these are covers several countries in Africa, Asia, as well as, and we had one grant in Romania, and we cover both R21 and R-01 grants, as well.

So the MIMH priorities, really, for global neuro AIDS research are to study the epidemiology and natural history of neurological and neuropsychiatric complications resulting from HIV and associated co infections, opportunistic infections, from a global perspective, evaluate relationships, if any, between HIV subtypes and neurocognitive impairment, and capacity building for neuro AIDS research globally.

So, we're fortunate that we'll hear from our panel some of their successes in this area, in addressing some of these priorities that we laid out for neuro AIDs research globally. So, we'll first hear from Dr. Ned Sacktor, and Dr. Noeline Nakasujja, who'll talk about her work in Uganda. I think it's mostly Noeline who'll be talking. Okay.

Ned Sacktor:
Hi, I'm Ned Sacktor. First of all, I'd like to thank both Kathy Michels, and the Fogarty, as well as Jim Han Joseph [spelled phonetically] at NIMH for the support they've given to us, to evaluate HIV subtype in risk of dementia in Uganda. And I'm delighted to be able to introduce Noeline Nakasujja, psychiatrist, in fact recently named Chairman of Psychiatry at Makarere University, who'll be talking about our studies from both the R21 and R-01.

Assessing HIV Subtype and Risk of Dementia in Uganda

Noeline Nakasujja:
It's a pleasure for me to be here. I would like to first thank Kathy, who looked out for me after [unintelligible] meeting in Morocco last year, to extend an invitation for me to come to this meeting. I'd also like to thank my other collaborator, Michael Boyvin [spelled phonetically], who helped facilitate my travel to this meeting, and to Ned Sacktor, who has allowed for me to make the presentation.

So, I'm going to talk to you about assessing HIV subtype and risk for HIV dementia in Uganda. I'm grateful to Fogarty to having facilitated part of this work. In work that we have conducted at the Infectious Diseases Institute at Makerere, in Uganda, we showed that the prevalence of HIV dementia ranged between 31 and 40 percent among ambulatory individuals attending the clinic. When we looked at individuals in that clinic that had advanced immunoseparation, with immensity [spelled phonetically] of 127 cells per microliter, we found that the prevalence of HIV , the risk for HIV dementia was higher in individuals who had plate subtype D, as shown on this graph here, in comparison to patients who had plate subtype A.

Now, in that group of individuals, 89 percent of the HIV positive individuals had HIV dementia with plate subtype D, and 21 percent had dementia of those who had plate subtype A. In a subsequent study that we conducted on 117 HIV positive individuals who had moderate immunoseparation with an average immensity of 233 cells, we found no difference in eh frequency of HIV dementia when we stratified by subtypes.

So given these results, we then decided to embark on a community cohort, a larger community cohort conducted in the rural western part of Uganda, in Rakai District. With an R-01 study, whose object are to access the association of HIV subtype and dementia

among 400 HIV positive individuals. And the 400 are divided in 2 groups, 200 who have moderate immunoseparation with a CD4 ranging between 351 to 500, and another group of 200 individuals with advanced immunoseparation who have a CD4 less than 200.

The second objective of that study is to compare the neurocognitive status of 400 HIV positive individuals, and 400 HIV negative individuals, and the third objective is to access to serve as a source for Alkali-Bladon [spelled phonetically] cerebrospinal fluid. So the preliminary results from this study are showing of the 194 HIV positive individuals that have so far been enrolled the majority of whom have moderate immunoseparation, the mean age is 35 years, and 35 percent of individuals have subjective memory complaints. A total of 83 percent of individuals have some form of hand, and this includes a asymptomatic neurocognitive impairment, mild neurocognitive impairment, but significantly, the HIV dementia percentage was at 23 percent.

Now, we have also been lucky to get to have 73 percent of the individuals, so far enrolled, accepting to [unintelligible] puncture, and we have storage of these samples. So, in some area, we'd like to say that hand is common in individuals who are antiretroviral drug naive, in rural Uganda, and when completed, this study will be one of the largest cohorts in sub-Saharan Africa specifically designed to assess dementia in relation to HIV subtype and level of immunosuppression. We will also be one of the largest CSF repositories for HIV positive individuals in Africa.

Our future studies will evaluate the association of HIV dementia, depression symptoms and neuropathy, and subtype response to antiretroviral treatment. We'll also assess whether the trajectory of neurocognitive impairment differs by subtype and level of immunoseparation after at initiation. And finally, we'll try to find the level of compartmentalized virus in CSF and it's association with HIV dementia. Details, if you need them, are on our poster, poster 57, you're welcome. Thank you for your attention.

[applause]

Jeymohan Joseph:
Thanks Noeline. We'll switch to work with the pediatric population. We'll hear from Dr. Barbara Laughton, who'll talk about neuro metabolite difference in basal ganglia and HIV infected children. Dr. Lawton?

Neurometabolite Differences in Basal Ganglia In HIV-infected Children Receiving ART

Barbara Laughton:
Good morning. I really appreciate the opportunity to attend this meeting. I've seen a lot of people and heard a lot of people talk, papers I've read, and I'm hoping we can have many discussions still before the storm hits.

I must acknowledge my collaborators. I'm a developmental pediatrician working in Capetown, looking at the longitudinal developmental and neurocognitive outcomes, and I was approached by Andre Van Der Kouwe at Massachusetts General Hospital and Anista Menkes [spelled phonetically] from University of Capetown to ask whether I was interested, or whether we could add a neuroimaging sub-study to the neurocognitive outcomes.

And the first question is, how do you get a five year old to lay still in an MRI scanner for an hour? It's not -- we would never get past ethics using any sedation or using anesthetic, but the, so we had, and R21, also part of the technology development in correction for motion that was added to this study, and used to compensate for the children that were moving.

And the first graph is actually looking at movement and different planes, and either rotational straight axis. And you can see here, the child moves and there's about a 12 millimeter difference, and if you're placing a voxel for spectroscopy, that tends to being a problem. Where you have flattened peaks and kind of widened curves where it will be, when you're trying to compare, you actually need quite a discreet measurement.

So our study used a subset of children from the Shur [spelled phonetically] trial, which was looking at children with different antiretroviral treatment strategies. We had to exclude -- we used one ethnic group, so we used the Kosa [spelled phonetically] children, because 80 percent of our children were Kosa. And we also had an infected controls form the same neighborhood who were on another vaccine trial that we could use, that we're also using in our developmental assessments.

The HIV infected children were randomly assigned to three different treatment arms. If their CD4 counts at enrollment was greater than 25 percent, and the early treatment arms were started before 12 weeks of age. The deferred treatment

antiretrovirals were only started when they were clinical or immunological indications, and the deferred, that arm was actually stopped in 2007 because of increased risk of early childhood death.

So in a way, it's a slightly historical arm with a bit of a survivor effect. We have small numbers. This is, the randomization was for the major trail which was, this is two centers. But this is, I'm told by my neuroimaging colleagues, this is quite a large sample for neuroimaging. As far as the age at scanning goes, they both were at variables, there was no difference between the four groups. And when we looked at the different neuro metabolites, there was actually no significance on innova [spelled phonetically], but then on a post doc assessment, there was some, there was a trained in the NAA and the choline compounds.

But what is striking to us, it was actually in the controls where the values, the mean values were lower, and this was, and the children who were on the early antiretroviral therapy were actually had mean values that were higher. Now, NAA is a marker of neuronal integrity, so you would sort of expect the controls to be better. And choline is also part of neuronal density, but and also turnover, so we weren't quite sure how to interpret this.

The other thing is we then went on to look at regression analyses, and there was a strong association in the deferred treatment with age and the older the child, the higher the NAA level, and we're thinking that possibly the children had damage earlier and showed recovery, but when you compared, when you controlled for age and you compared with the other arms, the deferred treatment arm was lower.

The other significant finding was just when we looked at a number of parameters, NADA CD4s, peak viral loads at various times, and the only significant effect was actually the baseline CD4 counts and CD8 counts at 7 weeks of age, and that was a predictor for the NAA and the choline at five years of age. With the lower the CD4 counts, the lower the neuro metabolites.

So just a summary of our findings is the NAA was, stands to be higher in the treatment, early treatment arms. I also haven't mentioned that those early treatments arms actually were interrupted, either at one year of age or at two years of age, and the choline was also tend to be higher in the treatment arms with, but and the CD4 seemed to be a predictor.

So, this is all very nice and very interesting, but what does it really mean? And our next step is actually to correlated with neurodevelopmental outcomes to see what's, kind of what level is actually important and has an impact on outcomes for the children. We have an RFO on R-01 where we will neuroimage again at seven and nine, and continue with neurocognitive tests. So watch the space, and hopefully we can give you some answers at the next meeting.

[Applause]

Jeymohan Joseph:
Thanks, Barbara. We'll now hear from Dr. Victor Mudenda [spelled phonetically] will talk about his work with subtype C neuropathogenesis work in Africa, and he and Dr. Charles Wood collaborate in Zambia. But Victor is going to talk about the work.

Neuropathogenesis and Neuroinvasiveness of Subtype C HIV

Victor Mudenda:
Give me a second. Right, thank you very much for having us here, I'm grateful that we moved into looking at the brain thanks to NIH. Previously, we had done work but was limited to looking at chest infections within the pediatric populations. So this is totally different now. We're not dealing with living bodies, this is post mortem work. Our target is for 400 postmortem cases. We have so far gone through 317 cases, so we have loads of brains and tissues to examine.

So in Zambia, subtype C is a clear type of HIV that is predominant, and our prevalence rate stands at about 14 percent. The cases we're going to look at today are those that are on the screen. I wanted to look at a few cases, and that's mostly for one reason. That like many other research bodies within Zambia, there were problems with transporting tissues across the borders, so we're delayed by about a year. But once we had started, we selected these few cases which were ART naive as the beginning of the beginnings.

What you need to note here is the age. Our people are coming to us when they are very, very young. More than that, they're coming to us, also have a look at the CD4 count. Very low CD4 counts. That says something about our health system, and we have passed it on to the clinicians to try and do something

about it. We are doing postmortem cases and therefore we have accesses to different regions of the brains that we stain. We use ordinary stains, hematoxylin and eosin. But further, we do immunohistochemistry in Nebraska. We also do a sequencing in Nebraska.

But in order to move in terms of capacity, but in order to move to be able to do things within Zambia, we have established an immunohistochemistry lab within Zambia. So some of this work will be done in Zambia. Right, so what you see on H and E, hematoxylin and eosin, which is a basic stain, essentially is what they commonly present with, which is meningitis, meaning that you have inflammatory cells going into the coverings of the brain.

If you look at the sections deeply, you will note that much of the inflammation is happening around the blood vessels within the brain. They cuff the blood vessels. In very few cases do you see the cells go into the neuropil, which is the [unintelligible] for the brain. Now, higher view here shows you the blood vessel, a pretty thickened wall, and then, hardly much is present within the neuropil, but if you look closer, as we did over there, you will see inflammatory cells around the blood vessel.

If you look closely at the parenchyma as well, you'll be able to see that around the cells, there is a space being created. This clear space, you need to be careful. Number one, it may be the result of inflammation and edema. Number two, it may be because the post mortem was done long after the person had died, and therefore, arthritic [spelled phonetically] changes has started to happen within the brain.

If we compare B and subtype C, B, these are the cases that are from Nebraska, and we look at C, which is from Zambia. The distribution of the virus is around the blood vessel. These brown spots, which reflect, you know, is a chemical staining. I hope you can see if from the back, if you can't, use the eye of faith. There's staining only around the blood vessel, but when you go to subtype B, you can see the staining goes deep into the parenchyma of the brain. That is one of the differences we noted.

And if you stain for CD8 positive, CD8 positive cells, T cells, the same happens. That you have staining around the blood vessels, we have three blood vessels here with distinct staining. If you get sections of the B type, the staining's

right within the parenchyma. Again, another difference we noted. If you look at microglia, microclear, essentially macrophages, which resident within the brain. Again, this is subtype B, lots of staining, lots of staining. Look at subtype C; hardly anything is present.

And then look at the astrocytes. If you use a marker against astrocytes and antibodies against astrocytes, something is happening again, similar to what you saw in microglia. That entire B, lots of staining goes on. Look at our type C. Highly limited. If you're someone with this up, astrogliosis, if you look at HIV positive, HIV negative cases in the Zambian cases, we had controls. You can see there's highly anything significant there. It's like what you find in the normal, is what you find in the infected.

So, to summarize this, we have, for the first time in Zambia, started see HIV cases, end stage HIV cases, we have noted the [unintelligible] spaces, and the ionization [spelled phonetically] of vessels. We've also noted that the P24 cells, which denote the presence of HIV, were just around the blood vessels. We didn't see any motion between the [unintelligible] cells as you would see in cases of B types. And then the microgliosis and astrogliosis was attenuated. And we have seen very few opportunistic infections, but we have done here only about 17 cases. As I have said, we have 300 plus cases to go. It is possible that some of these findings might change as we proceed with the investigations.

A little bit about the capacity building. So, some of this work requires to be done in Zambia. As a start, we have the immunohistochemistry lab that will set up and we have had workshops to train technologists to do immunohistochemical staining. Number two, we've had use of some of this material in setting up proposals for the Masters of Medicine students within the department. About three years ago, we introduced the Masters of Medicine in Pathology, and therefore, they're using this material now for their own stage proposals, which I think is a plus. And lastly, we also have somebody training to do sequencing in Nebraska. We have brought a sequencer, but it needs to train how to use a sequencer. So our hope is that much of the work that is being done in Nebraska will move to Musaka. Thank you very much.

[applause]

Jeymohan Joseph:

Thanks, Victor. So we'll move to the last talk, our Dr. Njamnshi will talk about peripheral neuropathy in studies in Yaoundé-Cameroon.

Peripheral Neuropathy in a Group of HIV Patients In Yaoundé-Cameroon

Alfred Njamnshi:
Thank you very much for inviting us to be here. Thanks to Fogarty, thanks to the NIH, thanks to Kathy in particular. Our focus was, with Georgette Kanmogne to locate hand neuropathogenesis and hand in Cameroon genetic variation. That was our major focus. But alongside this major focus, which we will not talk about it today, some of which has already been published, I'd like to share with you some preliminary data looking at peripheral neuropahty in some of the subjects that we have been looking at in our study.

The reason we looked at this side issue of peripheral neuropathy, it is that it's important because it disturbs the quality of life of the patient, and also is very associated with the lower adherence for antiretroviral treatment. It's common in Cameroon, and it's associated with HIV infection itself, and it can also be a complication of some of the drug regiments that are used for HIV treatment.

Very few studies have focused on this issue in Cameroon, and we know that AIDS, and the complications of AIDS are a particular problem in our country, so our goal was to find out the frequency and some characteristics of peripheral neuropahty in a sample of HIV/AIDS patients under our study in our department for hand. For our R21 we had looked at neuro AIDS one from 2007 to 2009, and in the R-01 grant, we've continued to look at these patients, and we've pulled together some of the patients in these two groups, to look at peripheral neuropahty. Patients were recruited consecutively, and we simply looked at the clinical presentations of peripheral neuropathy as a screen using the data that has been validated by the AIDS clinical trial group [unintelligible].

We compared HIV subjects with age and sex matched controls, and also looked at the treatment naive with the treatment group within the HIV group. This preliminary results show us the age and sex distribution of the sample. You would see from these that there are more females than males, and that corresponds to the demographics of infection in Cameroon, as well as globally. We found out that 18.1 percent of the 237 patients we looked at

presented with at least one symptom and one sign of neuropathy with the minimum age of 40. This data corresponds to a study that has recently been published in our population in Douala, finding similar results. The main symptoms of peripheral neuropathy are hypopallesthesia, ancohyperreflexia [spelled phonetically], and paresthesia, and the last one is very, very disturbing.

For these preliminary results, we tried to do some analysis, but again, I would insist that these are still preliminary, we have not looked at the whole data. And we see that age above 40, people with age above 40 are more prone to have neuropathy than those below 40. I must state that there were no signs, no symptoms of peripheral neuropathy in the age and sex matched control group.

When we looked at CD4 count, those that were severely immunocompromised were more prone to having neuropathy. Again, looking at the preliminary results concerning treatment, those that were on treatments regiments that had AZT were more prone to having neuropathy, as we know, than those who had other regiments. In conclusion, we see that peripheral neuropathy appears to be a serious problem in patients having HIV/AIDS in Cameroon.

As I mentioned before, these results are similar in Niyogi, compared with 21 percent that was found by our colleague Luma [spelled phonetically] and collaborators. So it may be more frequent in this population than suspected, and we need to pay more attention this. The main ART regiment type associated with higher frequency of neuropathy and HIV/AIDS is that concerning AZT, as we know. We need to, in future, to look at these patients, especially looking at nerve conduction studies, because we know that neurographic data precedes clinical symptoms, and if we can add more information to this clinical assessment, it might help us to develop more prevention strategies.

Again, thanks to the NIH grants and PIKanmogne, Georgette, who is here, our collaborators are there, and we want to appreciate the help that we receive from the Universities of Nebraska Medical Center, University of Yaoundé, Fogarty International. Thank you very much.

[applause]

Jeymohan Joseph:

Thanks, Alfred. So, before we open this up for general discussion, I wanted to give Dr. Georgette Kanmogne an opportunity to talk a little bit about her work relating to subtype differences in neuropathogenesis, from her work in Cameroon. Just a couple of words about it here.

Georgette Kanmogne:
Yeah, this will just be a brief presentation. I don't have slides. So I would like to thank Fogarty and NIMH for giving us support on this work.

What we've been doing in Cameroon since 2008 has been to look at the molecular determiner of HIV infection in the context of brain disorder and hand. And our preliminary published studies using structured neuropsychological tests, show that there is HIV associated neurocognitive disorder in Cameroon among infected patients, and it does get worse among AIDS patients. And these patients on treatment seems to have lower incidents.

And what we've been doing in our R01 grant has been to look at the effect of HIV subtype on viral neuropathogenesis, and we focus on recombination of type AG that is prevalent, the most prevalent subtype, not just in Cameroon but in Central and West Africa. Our preliminary findings, some of which are on poster 87, show that there is increased viral replication sickness among HIV subtype AG, compared to subtype B or individually A or G.

And we've looked at the effect of the virus or viral protein tight on the brain to tell us which are the major components of the blood brain barrier. And we see differential effect, with more inflammation and effect of andopathedes and all that enzyme that are most susceptible to degrade [unintelligible] metrics by subtype B, and not such major effect on subtype, both subtype AG.

So what we are currently doing is looking at epigenetic involvement. And what we see, there is some epigenetic changes with subtype B more likely to affect histone [unintelligible], especially histone four and three while there's differential effect of subtype AG. So those are preliminary data, which are, some of which are on poster 87, and the [unintelligible] I just presented is on poster 32. I will invite you to look at those posters, and again, I would like to thank the National Institute of Mental Health for supporting our study and the Fogarty International Center for the great support. Thank you so much.

Jeymohan Joseph:
Thanks, Georgette. So I'm going to open this up for general questions, yeah.

Female Speaker:
Thank you, panel, for an excellent presentation. I had two questions. The first is for Ned and Alfred. So in the peripheral neuropathy work we've done in Zambia, we're not, we looked at an ARV naive population and the key predictors weren't HIV stage, because everybody was advanced, but it was actually food insecurity and BMI. So did you see any association with anything nutritional in your study, Alfred? And Ned, do you think that could be a clade issue, or do you think it's an environmental issue, or?

Ned Sacktor:
Thanks. I don't think it's a clayed issue. I would suspect it's more likely environmental. Our actual frequency of neuropathy is a little bit higher than what Georgette presents, it's about 35 percent. Having some sort of neuropathy symptoms, but we haven't found, other than, I mean, yeah, basically we haven't found any specific risk factors at this point. We're about to look at that in our larger R01 study. Dianna Sailor [spelled phonetically] is leading those efforts.

Female Speaker:
And Alfred, did you guys look at nutrition or anything?

Alfred Njamnshi:
Thanks. We actually have some data on BMI that shows differences, but we haven't analyzed this with respect to polyneuropathy yet.

Female Speaker:
Oh, analyze it [laughs].

Alfred Njamnshi:
We should. We'll do that, thanks.

Female Speaker:
And my second is kind of a question or a comment, or maybe I'm speaking more to the program officers, but in terms of this brain injury mediated by cerebral malaria or other neuro inflammatory factors, not through the brain program, although I'm sure the infrastructure built by the brain program has helped. We've actually started the first of what I hope will be a series of clinical trials in Malawi, trying to target some of

these things that are, at least in observational studies, linked to long term brain injury, such as epilepsy.

So we have a study in place now, looking at entrolavaterasitum [spelled phonetically] during the acute cerebral malaria episode. And I'm getting ready to submit a study looking at more aggressive fever control, and if any of these actually show a beneficial effect, they're going to need to be scaled up. And I think to be scaled up meaningfully, they need to be transnational, it shouldn't just be limited to single country. So what those of you working in that area think about some sort of consortium.

I know there's a SMAT consortium, but I'm not sure that that's necessarily the right forum. Whether you think, you think, you know, your sites or your settings would be amenable to kind of a cross national, if we could find something on a small pilot level that could be processing, whether it could be scaled up within your site so that we had more of a kind of international look at effectiveness?

Male Speaker:
I'll just comment on that briefly. One of the things that I think is really helpful about a meeting like this is that you get perspectives from people working in very different areas. And it is, as a lot of us are doing studies where we're beginning to find things that we think may be useful and then how do you take that from your research study into public policy.

So just a comment that at the University of Minnesota, I started working with people in the School of Public Health and at the Humphrey Institute who do public policy, because it's not our expertise, and I think that may be one of the ways to get to this, because I think that even if we formed the groups, which I completely agree we should form, I think in each country, the way to make it work will be quite different, and that's where we need to pull in our colleagues who have that expertise, but, I completely agree with you.

Alfred Njamnshi:
The idea of forming consortia to run trials is really a good one, and there are two things. One, before that, actually they have been groups that in late 2007, 2008, there was a frontier of science meeting with a plan to try to see what are the next big trials. What are the next big interventions which can be conducted, say, in improving the outcomes of malaria? And one

of the things which was suggested was that at any one time potential people should look at specific interventions and get really big numbers in different sites, so that use specific and fairly large robust outcome measures to measure this.

Having said that, the phrenology of the disease is changing in very many countries. In some places, the numbers have gone down significantly. In others, it is almost unchanged. In others, the age group has shifted, so you have slightly older children in some of the places, but there are areas in different countries where there's still large numbers of affected children.

And so, in these areas, it's really possible to conduct some of these trials. Like in Uganda, we have more than 10 regional hospitals which admit very large numbers of patients and can run so many trials if they infrastructure for, like a clinical trial is improved. The same is true in areas in Nigeria and in parts of Ghana. So it's really, the potential is there, I mean, I think it can be implemented.

Male Speaker:
Thank you. Any other questions? If not, I think we have run out of time. I want to thank all of the speakers. We'll applaud, give them a hand.

[applause]

Female Speaker:
And before anybody leaves, I've been trying to deal with a snow situation so I haven't been paying, but I wanted to congratulate Dr. Damsche [spelled phonetically] on being the Central, what is it? The Central Republic Representative of Society for Neuroscience in Africa, the Central region? Is that correct?

Male Speaker:
[Inaudible]

Female Speaker:
Yeah, so congratulations.

Male Speaker:
Thank you very much.

[applause]

V. MINI-SYMPOSIUM: TOOLS AND TECHNIQUES: SURVEYS, SCREENS

AND SAVVY NEURO-ENGINEERING

NIH TOOLBOX: Diagnostic and Assessment Tools

Molly Wagster:
Good afternoon. I'm Molly Wagster from the Division of Neuroscience at the National Institute on Aging. I'm going to be moderating the session this afternoon on tools and techniques. And I'm going to start the session with a brief presentation on a set of measurement tools that were developed through the support of the NIH blueprint for neuroscience research and the NIH Office of Behavioral and Social Sciences Research. I've included several slides in this presentation that I will touch on, some of which I will touch on very briefly, or maybe not even at all, but I included them for your reference post conference.

This first slide represents the main distillation of features of the NIH toolbox, and if I don't make it to any of the other slides, this would be the one where the main take home message is. The NIH toolbox was developed under contract and Northshore University Health Systems is the prime contractor, with the main subcontractor being Northwestern University in Chicago. The effort was led by Dr. Richard Gershon. Through this effort, a set of brief, royalty free measures to assess four major domains of cognition, sensation, motor and emotion were developed, that in total, can administered in two hours or less.

Each individual domain battery is designed to take no more than 30 minutes to administer. All NIH toolbox measures were validated and normed for ages three to 85 and are available in English and Spanish. In addition to being a psychometrically sound set of measures, this was an extremely well-vetted effort, with over 250 scientists from 80 different institutions contributing to the development.

This next slide depicts a number of characteristics that NIH requested that the toolbox carry or have, which are shown on the left. Shown on the right are constructs that are measured with the toolbox instruments, and as you can see, they relationship a very comprehensive set of components for each of the major domains.

NIH and research stakeholders have long noted the lack of uniformity in measurement, and that exist both across studies, both domestically and internationally. This hinders our ability to share, to integrate, and to interpret results. And this is

neither efficient nor economic for the research enterprise. So tools such as those found in the NIH toolbox were designed to help maximize the yield from our research investment by providing investigators with a set of brief, valid, and readily accessible measures.

The slide -- excuse me, the measures were designed to assess health or function and to provide investigators with appropriate tools in order to avoid having to resort to the use of diagnostic tools or screeners for disorder or disease. I give an example of the mini-mental state exam, which often is used to assess cognitive function even in people with normal cognition. So this would allow people the opportunity to avoid those types of measurement tools when the purpose is really to -- of the research is to evaluate function and measure change over time.

The validation studies within NIH toolbox were conducted and published last year in a supplement to the "Journal of Neurology," and I provide the reference for your -- you can look at it in the future. All of these instruments were normed, and this norming process was done in over 4,800 English and Spanish speakers with the full spectrum of ages from three to 85. In addition, genetic material was collected in over 2,600 individuals who were part of the norming sample, and for whom there is the full complement of behavioral data collected. And I just -- to let you know, these resources actually are available for research.

The development of additional NIH toolbox translations is strongly encouraged. Helena Correia at Northwestern University serves as the translation manager for this effort. She has expertise in translation methodology, and has had years of experience guiding these efforts. And her contact information is displayed on this slide, and again, for your future reference when the slides are posted.

The NIH toolbox instruments are web-based and are designed to be administered by computer, with data imported automatically into a spreadsheet for analysis. The original contractors are currently developing a tablet-based version of these measures, which may be something more amenable to your particular situation in your country, and also for data collection as well, which is depicted here in this slide. There is not a specific date yet for completion of this tablet version, but this is expected to be available within approximately a year's time. To access multiple resources for the NIH toolbox, including the training manual, training videos, and other electronic learning

resources, and to keep abreast of developments such as the availability of tablet version, please visit the website at www.nihtoolbox.org.

I -- these are a couple of additional slides. I am not, as I promised, not going to spend any time on these. But these slides include information and mention of other measurement systems developed by NIH that may have promise for investigators supported by the Brain Disorders in the Developing World Initiative. I have provided a chart here depicting some of the essential features of these measurement tools, and this is also information on how to access the website for each of these. In addition to the NIH toolbox, a couple of other measurement systems you might be interested in are the Patient-Reported Outcomes Measurement Information System, or PROMIS, and the Quality of Life in Neurological Disorders Measurement System or Neuro-Qol. Thank you.

[applause]

I'm now going to introduce the four speakers for this session. As just a reminder to the audience, all questions should be held until the end of the -- after the speakers are through during the panel discussion component. So our speakers -- I'm just going to introduce them in order, and then they will introduce themselves a little in more detail are Dr. Kieu Phung, Dr. Daniel Mamah, Dr. Steven Schiff, and Dr. Brian Forsyth. And Dr. Phung, you first.

Dementia in Lebanon

Kieu Phung:
Thank you very much. My name is Kieu Phung, and I'm from the Danish Dementia Research Center from the Department of Neurology, Copenhagen University Hospital, Rigshospitalet in Denmark. And this study is a collaboration between the Danish Dementia Research Center, DDRC, and the 10/66 Dementia Research Group from the Institute of Psychiatry, Kings College, London, and the Department of Epidemiology and Population Health from the American University of Beirut. And I am very honored to present the study on behalf of the leader group [spelled phonetically] of the study, which includes the contact PI from the AUB, Professor Monique Chaaya, who is present here, and co-PI, Professor Gunhild Waldemar from the DDRC, and she's also here with me in the audience. So I'm really honored also to be able to present the studies to all the brains around the world

who work together to promote better brain health in the developing world.

So as we have heard through many sessions, there are certain brain disorders that are more common in the developing world than in the developed world, but dementia doesn't discriminate between low and middle income countries and high income countries. On the contrary, due to very rapid demographic aging in the developing world, it is the developing world that is sharing the heaviest burden of dementia, as 60 percent of people with dementia are living there. And the rate of increase is projected to be much higher for the low and middle income countries than for the high income countries. And on the other hand, only 10 percent of the research has been done in that area, hence the name 10/66 -- sorry, 10/66 Dementia Research Group. [unintelligible], okay. I have to go back.

Okay, so in the Middle East the number of people with dementia is supposed to increase very dramatically over the next 20 years, but there is the scarcity of research, and there is a lot of social and health polices to cope with the public health problem, and there is no evidence-based knowledge in order to guide prevention and interventions. Therefore, it is very hard to compress years of hard work into five minutes, so I'm going to deliver you only a little appetizer and you have to get the main course at the poster number 15. So if the talk is cut short it would make you be more curious and visit the poster. [laughs]

But the overarching goal of the study is to establish the first longitudinal community-based cohort of 2,500 people older than 65 to study dementia occurrence risk and protective factors specific to the Lebanese population. The specific aim of this pilot study, which was funded by an R21 grant from the Brain Program, the first aim was to validate education and culture-fair completive assessments in Arabic.

The 10/66 Dementia Research Group once staged [spelled phonetically] diagnostic assessment for dementia and two brief cognitive screening instruments, the RUDAS and the IQ code. The second aim was to carry out a pilot study to assess the feasibility of the large -- conducting the large longitudinal community-based studies into governorates of Lebanon in order to generate preliminary data about dementia prevalence, collect information about access to care, care arrangement, co-morbidities caregiver burdens, as well as risk and protective factors for dementia.

So it is very interesting that my talk just follow the toolbox sub-talk, because the 10/66 Dementia Research Group used the same diagnostic assessment and the population-base methodology, therefore allowing directly comparable studies in order to compare the differences of dementia occurrence across regions of the world in the developing world. And through that, perhaps it would help us to review new risk and protective factors in order to design more effective preventive strategies.

And this study is the first to validate three education and culture-fair cognitive assessments in Arabic for research and for clinical practice. And at the individual level, the validated cognitive assessment will pave the way for better detection, diagnosis, and management, and in-depth knowledge about the circumstances of people with dementia and their caregivers, will guide intervention to better support them. And at the institutional level, the AUB will continue as the research and training institutions to provide the knowledge to improve clinical practice and design effective preventive strategies. At the policy level, the Alzheimer's Association Lebanon will facilitate the knowledge transfer to the public and policymakers to raise awareness, de-stigmatize dementia, and influence public policies to provide better access to health care and social protection for people with dementia. At the regional levels, this study has created a ripple effect. So now you -- we have researchers from the Kingdom of Saudi Arabia and Egypt who expressed interest in establishing similar cohorts in their countries.

So in order to conduct a study we need, first, the funding, and second, to build capacity for the local researchers in Lebanon. And I extend many thanks to the Brain Program which has provided us the necessary financial support to carry out the study. And the capacity-building built on the available expertise at the American University of Beirut, and they already have very excellent epidemiologists and clinicians who are experienced researchers. The Kings College, London --

So we took a multidisciplinary approach and there was cross-training of collaborators, and we involved both NGOs, such as Alzheimer's Association and the IDRAAC, which is institution directed to promote mental health in the develope -- in the Arab world. So -- and the DDRC provided the training in dementia epidemiology, cognitive testing, and dementia diagnosis and care. And now the Lebanese team has had a very solid multidisciplinary team to carry out this project further.

So basically, the validation study have proven that the assessment we have done, we have validated very good instruments and I will explain more to you when you visit the poster. And the prevalence study have shown -- we have finished data collection from three -- two governorates of Lebanon in a random sample of 510 [spelled phonetically] person, and the preliminary prevalence show a 10 percent prevalence of dementia, which is high compared to other parts of the world. And thank you for your attention.

[applause]

Identification of Psychosis Risk Traits in Africa

Daniel Mamah:
So -- well, first of all I have to apologize. I kind of lost my voice. I'm coming off a little cold. So hopefully it's not really going to affect the talk too much. Our -- I'm actually from the Washington University in St. Louis in the Department of Psychiatry. Our project is in collaboration with [unintelligible]'s group at the Africa Mental Health Foundation in Kenya. And our project is studying prodromal symptoms in Africa. That's pretty much what we want to do. So basically trying to identify the prodromal state of psychotic disorders.

Now why is this important? We probably all know what psychotic disorders are: schizophrenia, schizo-effective disorder, effective psychosis. And what we may not always be very aware of is what the prevalence is. So we're really talking about a 3 percent lifetime prevalence of psychotic orders. So it's a real significance in our society. And so the question is, you know, what can we do for individuals who have psychotic disorders? How can we alleviate the burden of this problem? And so, our strategy, our long-term goal, is to try to intervene in the prodromal states, because there is a lot of research that talks about the prodromal states being a really good sort of time to intervene. So the earlier you intervene in these individuals the better your long-term outcome is.

So in the last few years there have been a lot of studies about the prodromal schizophrenia, and typically the prodromal involves attenuated psychotic symptoms. So you may have psychotic experiences that do not actually rise to the extent of psychotic disorder. The tools that have been used over the past few years have been somewhat problematic. Individuals who have been predicted as being a prodromal don't always end up becoming

schizophrenic, and so this really is a problem because how do you intervene in people who don't necessarily transition?

In fact, more people do not transition than do. And so this is something that we've been trying to study in Africa, because it really hasn't been studied too much. And the question is, how can we improve the ability to predict individuals who will develop psychotic disorders, individuals who get worse? And we've used a variety of tools in the past that have really been perfect in Kenya. And this kind of led to the development of improved -- what we think is an improved tool, something called the work-up screen. And I'm going to just really say something very briefly about it. We think it is -- it's a little bit more cross-culturally applicable than some of the other tools out there. And it's a 16-item questionnaire, half of which is supposed to predict psychotic experiences, the other half to predict the bipolar disorder. So this is kind of what we used.

Our project involves a longitudinal study. We initially screened 2,800 secondary school students in Machacas, Kenya. Machacas is kind of unique. It's pretty close to Nairobi. It's unique because it has both rural and urban components, so you can kind of look at the effect of different communities in Kenya. The study's a longitudinal one, over 20 months. And the goal is to periodically assess individuals. So we have the DIS where we try to identify co-morbidities. We have computerized cognitive testing, tests of neurological function and dyskinesia; we also assess stress burden, as well as anthropometry, which is measuring facial dimensions.

So we're kind of -- we only have preliminary baseline data to present, but there were some interesting findings. First of all, kind of the prevalence. If you kind of look at the entire population that we screened, what do we see? And the first graph there kind of tells you the prevalence of different frequencies of occurrence of individual symptoms on the work-up screen. And what you can see is about 5 to 10 percent of individuals reported having at least one frequent psychotic experience, as well as affective experiences. We also noticed some gender differences: not very surprising. Women tended to be -- to have a little bit more endorsement of -- tended to have a little bit more endorsement of affective symptoms, while males had a little bit more of the psychotic symptoms. I know it's not very clear, but the symptoms on the right side of the chart are the psychotic symptoms, those on the left are the affective symptoms.

Okay. There were also some cultural differences. Individuals, when we compared the study to individuals in the U.S., they tended to have a little bit more affective symptoms than those in Kenya. However, when we look at the associations between different traits, we didn't quite get the findings that we thought. Cognitive symptom didn't really appear to be more abnormal in the psychotic risk individuals. It's not quite clear why that is, but you know, we're still doing some baseline evaluations, and you know, maybe longitudinally, you know, more abnormally, more cognitively abnormal individuals will give us different information about who may transition to psychosis. And one finding we did find, though, is the degree of stress was more in individuals with psychosis. And here in this chart you can actually see that there was some kind of stressors that were endorsed more by people with psychosis risk, things like how people treat you, themes that have to do with dying. So we thought that was kind of interesting.

And just to kind of wrap up, in the future we hope to get more information regarding longitudinal assessments, how to trace change over time, and we would like to go beyond the allotted two years that we propose; what happens after three, four, five years? We're also doing some studies in Rwanda, so it will be interesting to kind of compare different African countries. And then, finally, the most important thing that we're trying to strive for is, how do we intervene in these individuals? How do we get them better? And so we have a few proposals that we hope to share with NIH this year, and hopefully we'll get some -- we'll get the ability to try to test that. Thank you.

[applause]

Molly Wagster:
Dr. Schiff?

Volumetric Brain Analysis for Hydrocephalous and Epilepsy

Steven Schiff:
Thank you. Thanks very much for the chance to talk here. We can -- do we have slides? Yeah. So most of what we'll discuss today is funded by the Fogarty International Center, and we have some support from other centers at NIH as well.

Motivation for this: a number of years ago the Children's Hospital in Mbale, Uganda, the CURE Children's Hospital, is

looking at an experiment in comprehensive epilepsy care. And most of the world's epileptics live in regions where they will never see a cryogenic, high-field MRI scanner. But MRI scanning is part of our guidelines, our treatment standards for selecting pharmacologically-intractable patients for epilepsy surgery. So in their evaluation of this kind of internal scarring in the hippocampus, you simply can't see on a CT scan. There's an old rumor from air studies that you could look at the size of the CFS space, it would be larger with epilepsy; those conjectures are not borne out by data. So much of this is done at a small pediatric specialty hospital in eastern Uganda.

The other motivation for this was one of Ben Warf's previous studies where they looked at the neuro-cognitive development in children treated for hydrocephalus who had mild [unintelligible]. We have a variety of ways of measuring hydrocephalus -- this represents distances that we call a frontal occipital horn ratio -- but what we found is that these measurements that we make more are a measure of the degree of hydrocephalus, the amount of fluid. They don't actually measure the amount of brain, and perhaps not surprisingly, they don't correlate very well with neuro-cognitive development. Brains do the thinking, the fluid is a mechanistic problem that causes the disease.

So we began at first looking at animal models. This is a hydrocephalic infant mouse, and this is a wild-type mouse. This -- the growth is stunted and the head is domed by hydrocephalus. I create these with aluminum silicate, but very much we're interested in introducing the organisms. We have a large program to look at the infectious agents and post-infectious hydrocephalus and neo-natal sepsis in Uganda. And we're very interested in taking putative agents that we identify, and began exploring the mechanisms of infectious hydrocephalus.

The other thing that comes up at this meeting, which I've been quite interested in, are all of the talks about malnutrition and cognitive development. And one of the things that we're able to do now with the tool, as I'm about to show you, is to look at brain volume. We are both -- whether you're treating hydrocephalus or malnutrition, we're in the business of growing brains. And I throw out as an open question whether some of this effort is also useful in learning how to best grow brains in children with hydrocephalus. I run an engineering center now, and we literally stole some of the flight control algorithms from things like autonomous air frames and used them in order to track the more complex outline of human brains.

Doing this is in mice is rather easy, because the brains are smooth. And I actually put a book out on these techniques in 2012.

What we found, using the pediatric database that NIH now has organized of normal infant development, we ended up showing that we could create human brain growth curves from images and we use this with techniques that work with either MRI or CT. And we did the CT growth curves. All of you, of course, know about the head growth curves, and interesting there's about a five-centimeter gap of growth from head circumference that has little to do with brain growth; it's a thickening of the skull on scalp. And it's -- I always think it's fun to watch these algorithms work. They literally fly around this rocky landscape, just as we can get air frames to do.

And what we find in children in Africa who have been treated -- this child, you can see the sunken fontenal after getting an endoscopic procedure that Ben described yesterday -- the children in green are doing better developmentally. They have larger brains. The smaller-brain children do worse. But that's not the only effect. The more spinal fluid that's in there, the more stretching of the brain, the worse they do cognitively. And we see this in multiple ways. We have a Fogarty-funded Phase III randomized surgical trial comparing shunts and endoscopic techniques, and our question is, which is better at neuro-cognitive development, and can we do this? Can we predictively take a patient -- they generally come with small brains with bad hydrocephalus -- can we now optimize the target trajectory so we know how to manage these children over time, because we know what their brain growth should be?

The other question that comes up is how many times do you want to radiate this infant? This is the worst possible case of newborn infants getting CT radiation. And we actually have a nice program starting here to introduce very low-field MRI units for a relatively easy condition to image. And Jonas Abungelok [spelled phonetically] will be the new department head of Biomedical Engineering at Mbarara University. So we're trying to seek establishing this as an African technology.

And lastly, just for a few seconds, we've applied this to the problem of the epilepsy cases. And it all depends on the volume of the opposite temporal lobe. If you leave a large normal temporal lobe in place your patients tend to be seizure-free, as opposed to if you don't. This is bad situation. Similarly, the whole brain volume becomes critical, because patient's who've

had a global loss of volume, what you don't see if you look at the symmetric sides on CAT scan, or have had hemispheric involvement, will do worse than patients with large, residual brains.

Then the only other comment I'll make is everything I talked about today is applicable to health care in the industrialized countries, as well. We manage both -- patients with both hydrocephalus and epilepsy, and all of these volumetric techniques forced on us by the presence of CT scanning are techniques that we can use in U.S. health care. Thanks very much.

[applause]

Molly Wagster:
Dr. Forsyth?

International Guide to Child Development

Brian Forsyth:
Thank you, and good afternoon. First I'd like to thank Dr. Kathleen Michels and also the Danuta Krotoski from NICHD, but all the staff who support this work that we're doing, and support this conference as well.

This -- the title that was given in the conference was a little bit short in that this is a guide to monitor and support child development, so not just development of an international guide in child development. Ilgi Ertem is my co-principal investigator from the University of Ankara in -- Ankara, but also, I want to speak about the other investigators, because this is actually a study that's being done in a number of different countries. So there's Vibha Krishnamurthy from Mumbai in India, and Empeli Melodsi [spelled phonetically] from South Africa, Pretoria, and Genina Squasero [spelled phonetically] in Argentina.

I don't really need to state again, it's been said a few times, the impact of child developmental disabilities, not only on the individual child, but also on countries and the economies of those countries for the future. But currently there is no accepted -- globally accepted means of assessing child development. There are instruments that have been taken from the U.S. or from Britain and applied in countries, but there is nothing that has been developed from the ground up across countries.

The guide to monitor and support child development, the original one, was developed by Dr. Ertem in Turkey with an R21. It's an open-ended, pre-coded 10-minutes interview. And it has a conversational style that improves communication and partnership between the provider and the caregivers. It allows for the development of therapeutic alliance, rather than the parent being -- feel that they're being tested on their child's development. It's easy to learn by physicians and community health workers, as well.

So the aims of this study were, first of all, to standardize the GMCD, the international GMCD in four countries that have very different demographic, cultural, linguistic characteristics, so as to make it appropriate for international use across countries. And so, as I said, it's being done in Turkey, India, South Africa, and Argentina, very different countries.

The second phase of the study, which I'm really not going to talk about -- I'm just talking about standardization at the moment -- the second phase is being done at the moment, and that's establishing the validity of the international GMCD. I should have said that this is the other end of the age interval from the toolbox. This is the birth to three and a half years of age, where the toolbox only started at three years of age.

And then the third phase of this study is to conduct a pilot study in the four countries to assess implementation and sustainability, and whether in assessing children's development, anything can actually be done for these children. I said at the beginning that the -- it also includes support for child development. And here it's tied to the WHO care for child development, which is an intervention to help stimulate children's development.

In the standardization phase, there's a brief questionnaire with the patient that includes socio-demic information, and importantly also includes measures of depression and also food insecurity, two things that can be affecting children's development. Then there's questions to establish the normal health of the child, because if you're going to think about assessing normal development, then you want to rule out from your sample those reasons that might affect children's having poor development. And then the GMCD is provided to the caregiver, so usually a parent. There's also measurements of the height -- weight, height, and head circumference, and we've already heard before about how malnutrition and stunting can

affect children's development. And a hemoglobin is done in a fingerstick sample.

And so there's the use of a prescriptive sample. In other words, obtaining information, but then not using for standardization all those children who you think could have developmental delay, or at least have factors that impact on their development. So anemia, hemoglobin of less than 10.5, birth weight of less than 2,500, growth less than the third percentiles, and any predefined illness, such as HIV for example in South Africa; and then also perinatal illnesses. So those children we got information on, but excluded from the sample.

And this is the results of our enrollment so far. All of the countries have actually surpassed what we considered to be our sample for doing this for all different ages of the children up to three and a half years of age. But you can see there was a very high exclusion rate from the prescriptive sample. For example, in South Africa, where a half of the children needed to be excluded from the prescriptive sample, one-third of those children had a hemoglobin below the age -- below 10.5. And in India one in five children was below the third percentile for one of the growth parameters. And I will just say, in India we actually had to enroll in-private physician offices, because when they tried to enroll in the public clinics the exclusion rate was so high that we were never going to get there with our sample. All of this needs to be controlled for.

Uh-oh. So in summary, getting to the final slide here, adherence to the prescriptive sample and the exclusion of large numbers of subjects has caused problems with achieving the necessary sample size. And so enrollment has to be extended to do that. I will note that here we are, trying to get approximately 12,000 normal children, or so-called normal children, as opposed to what was in the toolbox of only 4,800; that's because we're doing it across countries. There's very good results with the majority of the items, which are shown on the poster which are showing the curves of development. And the countries for most of the items, development is at the same.

But it's the differences that are important, it's the differences -- when a development is different in different countries that highlight the need to develop one instrument across countries rather than taking something that was developed in just one country. Obviously we need to do further analysis, because of those factors that affect development, and we already

see that in our results, of things like anemia affecting the development of these children.

And then final decisions about inclusion of items to be made by an expert panel of developmentalists, as well as statisticians will review all the results to come up with the final instrument, which should be available later this year. Thank you very much.

[applause]

Panel Discussion

Molly Wagster:
So we're going to move to the discussion and question and answer portion of this session. I'm just going to briefly introduce our discussants, Dr. Gretchen Birbeck from the University of Rochester, Dr. Leslie Davidson from Columbia University Medical Center in New York, and Dr. Narendra Arora, who is affiliated with the Public Health Foundation of India, and serves as executive director of the INCLEN Trust International and Child Health Research Nutrition Research Initiative. So I will let them decide who will go first, but I'm hoping that we can hear a few comments from our discussants, and then open the session to questions. Dr. Birbeck, did you want to make some initial comments?

Gretchen Birbeck:
First of all, thank you for your lovely presentations. I think the only thing worse than having to develop an instrument is not having the instrument you need. So I'm -- I find instrument development one of those ugly tasks, and so I'm very excited about the idea of international -- developing instruments that are cross-culturally valid and could be used in multiple settings.

I think, in addition to some of the presentations that have gone on, I think that as technology is rolling out we're becoming more and more aware of our lack of normative data, and so one of the endeavors that we've taken up in Malawi that I think has been very successful is trying to get normative data for imaging. It's not a huge problem, because I think most of our environments don't have a lot of technological, highly-technical imaging, but when you suddenly do get that technology, the lack of normative data actually prevents you from being able to institute it clinically, and it also prevents you from knowing what to do with research.

And so, as an example, when we were able to bring neuro-imaging into Malawi for research purposes -- and of course it was also used for clinical purposes -- within the first year we ran into the conundrum of, we were seeing a lot of non-acute MRI abnormalities in children who were acutely ill. And so how did you put that together? And from a research perspective we were running into the same. We were seeing strange vermian atrophy in children, not something I'd seen very much in the U.S., such things. And so we stepped back and realized that until we really knew what normal looked like in that population, we couldn't interpret the information from our imaging either clinically or from a research perspective.

We were able through funding from the Brain Disorders Program to go into the community and get a representative sample of children, and bring them in for imaging and lo and behold, 17 percent of them had abnormalities, which really far extended what -- exceeded what one would have expected based on U.S. norms. I think this is an example of something that the Brain Disorders Program supported. When I told people I was writing a grant to get normative data, they took -- first of all, they fell asleep and then they told me no one would fund that. And of course, that's not true. [laughs]

But I think this is an example that as we get more technology and do more investigations we come back to realize that, unless we can measure what we're interested in and that we know what normal is, we find our hands tied over and over again. And trying to simply transplant the norms from elsewhere, transplant the tools from elsewhere is an incredibly limited approach. And so I'm really pleased by what the presenters today have described.

Molly Wagster:
Thank you. Would anyone else from the discussant panel care to comment on the presentation?

Leslie Davidson:
Yeah, a little bit more of a dilemma among the riches, because you reported on the toolbox, which has elements for children, more thorough assessment, two hours or so -- up to two hours it said -- looking at a motion-cognitive motor and sensory. Narendra reported on the work they've done in India, being used all over India, looking at child development with a sort of a categorical division. Your [spelled phonetically] reported on the work with Turkey and other countries, Mumbai, et cetera, on

what looks like, I think, a developmental trajectory more than a categorical to be used cross-country -- yours to be used cross-country. I mentioned yesterday the UNICEF work on a toolkit for assessment of children cross-country, and the Washington group of statisticians are looking for a screening measure to use across the whole world. And so the riches are all of those things, building on early, early work that we did with the TQ, and other people did using the Denver and different places.

So, I'm at sort of a "now what," putting-it-all-together place, because there's similarities, differences -- I'm not quite clear on the range of your guide to monitor and surveil. Where should we go now, because we have all of these parallel developments and I wonder what's going to happen next as we move to that next stage, particularly since we're all talking about cross-country and cross-cultural comparisons. And I'd love to have more time than we will have to be thinking about that; that maybe something that Fogarty wants to look into, to sort of scrutinize more fully in the future and elaborate on what can be used for which type of study.

Molly Wagster:
I think you make some excellent points, and I'm sure Kathy and others may be able to think of some creative ways that we can bring people together, maybe even with a working group to start discussions and start things going. Dr. Arora?

Narendra Aurora:
Yeah. Thank you very much. First of all, thank you, all the presenters, for this excellent presentations. I would, again, reemphasize and endorse what Leslie said just now, that the need for standardizing the efforts which are going all over the world in different parts, resource constraints and resource-competitive environments. And this will certainly be a very, very welcome idea.

I have two or three other, additional points. The whole area of neurological and mental disorders is associated with a stigma, and we have been hearing that this is in every culture, also particularly in developing countries, the stigma is an important issue. And therefore whether screening tools or diagnostic tools where the gap in diagnosis and treatment is over 80 percent -- I was hearing a report from China yesterday that 80 percent gap. In a situation like this, when these tools are being prepared I would rather look at specificity than sensitivity. The reason is that if I pick up too many false positives, the whole program is likely to fall, crash down. And

therefore when these instruments are developed we need to focus a lot of attention on how to see that minimum number of false positives are, because they are -- the risk of being stigmatized is there.

The second issue is -- and which I was very pleased to listen when you opened the talk about this NIH tools -- this whole issue of a royalty which needs to be paid. At the moment I think this is one of the biggest barriers in access to care for a lot of these brain disorders. For a North American, 50 cents may not mean anything, but for us it means all. And it creates such a barrier. And the other important component is that if there is a royalty attached almost be certain that such -- no public health program can be brought in, because in public health we need to have -- we don't know how many have been screened, what his diagnosis.

So there is absolutely imperative need that we need to have tools, both screening as well as diagnostic, which are open access. And if we really want, it could complement -- and I think all of us are working towards this -- to de-mystify the brain disorders. I think there are not sufficient neurologists, psychologists, clinical development pediatricians anywhere in the world. And while the problem is such huge; therefore there is need for demystification, and so that lower level can come up.

And finally, the point from Lebanon was made that probably mobile health technology may be used for screening purposes so that even populations and communities can be involved. And I think this mobile health should be more effectively and efficiently utilized. Thank you very much.

Molly Wagster:
Thank you. I think those were excellent comments and thoughts from the panel. We have just a few minutes for some questions from the audience. Yes, sir?

Male Speaker:
Yeah, Mike Boyven [spelled phonetically], Michigan State. I know that initiatives that seem to be broad-based, more global, or international in their approach in developing the universal end-all, be-all neuro-developmental assessment are attractive. But really the proof is in the pudding. Molly with regards to the NIH toolkit, Professor Forsyth with regards to the developmental screening tool that you're developing, what kind of sensitivity, what kinds of specificity, what kinds of

correspondence validity is being pursued to validate these before we summarily dismiss the transplanted tools? Yeah?

Molly Wagster:
I'll make one comment about the NIH toolbox measures. As I mentioned in my brief remarks, these were validated and normed in, of course, U.S. population census-based samples. And they -- however, the instruments were designed from the start to be a way to assess health or function, and not originally -- normed -- validated and normed in particular patient groups. So at this time -- that was the purpose of the contract, and those are the goals of the contract. And they were met.

This was, again, a way to give investigators a way to use instruments that -- and to stay away from diagnostic tests or screeners in order to measure function over the lifespan and measure change over time. But we do encourage and are actively encouraging individuals to take these measures and validate them in particular patient populations -- in children, adults, older adults -- and we hope that that will build, you know, and make the use of the NIH toolbox even richer. But I do want to clarify that at this time the instruments are for assessment of health.

Brian Forsyth:
Excuse me. As far as the guide goes, the validation phase of the study is just ongoing at the moment. So it is being studied against or validated against an extensive evaluation of children's development that includes the Bayley, both Bayley 3 and Bayley 2 items, as well as other child developmental assessment. So that's being done at the moment in the four countries. So in the four countries and the different languages, obviously it would be nice also to validate it in other countries as well. Thanks.

Molly Wagster:
One more question.

Male Speaker:
Yeah, Jonas Geda [spelled phonetically] from Mayo Clinic. I think the NIH toolbox, the -- what is attractive is that it contains cognition, emotion, motor -- the whole package together, because usually these things are so separate, we have to hunt for them in different areas. And definitely this will be attractive to use it in developing countries.

One thing I want to know is, there is -- you provided a resource for translation. So would that include only translation to Spanish, or you know, it can be translation work in different countries. I mean, there are so many languages in the world.

Molly Wagster:
It is all -- excuse me. The NIH toolbox measures already have been translated into Spanish, so that is available. The individual whose name I put up there would assist investigators with preparing for and setting up to translate into other languages besides Spanish or English.

I think I'm correct, Kathy, in that we probably need to wrap up this session for -- two minutes, all right. Well, one more question? Yes.

Maryanne Romski:
Maryanne Romski, Georgia State University. It's really not a question; it's really a comment about what I'm hearing. I think it's exciting, all that's been developed, but to me it begs the question of where we go next, and the fact that interventions that can target the needs of the individual children that are identified is critical to moving forward in terms of treating the children we identify.

As I was looking at the children with hydrocephalus, I was thinking about early interventions that could indeed -- behavioral interventions that could indeed, perhaps look at whether or not one group of children were able to benefit more or less from treatment. And I think that really has to be next steps as we move forward in thinking about identifying children. We have to have a place to go after we identify them.

Molly Wagster:
Thank you for your comment. And I just want to thank all of the speakers and the discussants for this session. Thank you.

[applause]

VI. Plenary: Basic and Animal Research

Female Speaker:
So I'd like to welcome the next session panelists, if they can come up on the stage. About -- the next session is on animals in research in the developing world. And Dr. Sharon Juliano will be moderating and keynoting this session. Oh, and I was supposed -- there was a flash drive that was found that's up --

so if you've lost your flash drive it's on up at the front desk. Go ahead. Yours, Sharon.

Animals in Research in the Developing World- Lessons and Opportunities

Sharon Juliano:
[laughs] Okay, thank you very much. Before we get started I just wanted to thank Kathy and the Fogarty Institute for having this session. I think it's really important, and I think it's really great that this was organized, and I'm really -- I really feel honored that Kathy asked me to speak about this. So I hope I do her proud for doing this. And I would also, again, before we get started, I'd like to introduce the people on our panel. And I was just kind of introduced to exactly who they are a few minutes ago.

So let me just say we have Vivienne Russell, who I do know very well. And Vivienne is a professor at the University of Cape Town. She does very interesting research. She is what she will tell you about, and she is also soon-to-be a professor at the University of Kwazulu-Natal. And then we have Fleur Howells, who I also know a little bit. And Fleur is a new assistant professor at the University of Cape Town, and she also does translational-type of research, which she's interested in trying to understand mechanisms underlying various psychiatric diseases. And then have -- and I'm actually -- so we have Rodolfo Goya. Can you raise your hand? Okay. And then Rodolfo Goya is a senior scientist at the National Research Council of Argentina, and he leads a biomedical research group devoted to studying the neuro-biology of aging. And then we also have Reinaldo Oria. And he is at the Federal University of Ceara in Brazil. And I'm sure he will comment on what he's been doing.

Okay, so thank you very much. So, okay -- okay, knocked something down there. Okay, so what we're going to talking about today is animal research in the developing world. And I put up those credentials of mine where it indicates that I've been the chair of Ethics in Research at IBRO, which is the International Brain Research Organization, and I think that's been mentioned a couple of times already. But what this has done has allowed me to visit a number of countries throughout the world and to talk to people about doing animal research. And I'm currently not doing that anymore, but I'm still kind of visiting a lot of places and also participating in IBRO as the chair of the U.S. Regional Committee.

So, let's see -- yes, okay. So I thought what I would do is I would really like to talk primarily about the places that I know, okay? So I know Africa the best; so that's where I'm going to focus my work -- or focus this talk. But I also wanted to talk a little bit about Latin America, and especially since we have some representatives from Latin America on the panel. And I'll get back to that in a minute.

So if we start with Africa -- so Africa is -- let's see, does this work? Yes, okay. So Africa is a big place. It's a very big place. And in most of the countries that you see here, most of the countries are doing some type of animal research. And the type and quality of animal research varies dramatically throughout the continent. Now the first thing I'd like to do is sort of talk or mention a little bit about what is wonderful about doing animal research in Africa. And this picture kind of gives you the -- one of the ideas.

I mean, there's a few things I'd like to mention, but this photograph was given to me by Paul Monger [spelled phonetically], who works in South Africa. And he and his colleagues do a lot of research on a bunch of -- or 'bunch' -- many different species. And in Africa, as I'm sure you're aware, there is an amazing diversity of animal species, and for -- this is one of the really important reasons that we need to study animals in Africa. And I just want to mention that this is a montage of a number of animals that was put together by Emadia Hunwo [spelled phonetically], who also works with Paul Monger now, and he's originally from Nigeria.

So there's a number of different species. Now this -- I have a few slides that were given to me by Paul Monger and his colleagues. And this is, I think, really interesting is that he's -- he was able to acquire an elephant brain, and this is an MRI, or several images taken by MRI from the elephant brain. And what he's tried to do is look at neuro-chemically and neuro-anatomically, he's tried to look at different features of this elephant brain and see what's novel or interesting or important about that. And this is some examples. So this is the cerebellum of the elephant stained with different types of stains. I think this is just a Nissl stain, and this is a bunch of different immuno-reactivities, neuro-chemicals. And he's found evidence that the cerebellum of the elephant has some features of very complex circuitry that's different from other animals that he's looked at.

Then he's also looked at the hippocampus of the elephant. And he's also found that that also seems to have some distinct features that are different from other animals, and that this animal, the elephant, seems to have features which demonstrate adult neurogenesis. Now the concept of adult neurogenesis is a novel one, as I'm sure you're aware, and very interesting, and one that's really been followed through systematically by a number of the researchers in this group. And Emadia Hunwo is one of the ones who was working on that.

So another thing that this group did was they looked at -- in this case they looked at the brain, but they also looked at the retina of giraffes. And one of the things they were interested in, because a giraffe is obviously looking from such a unique vantage point, if there was something specifically different about the eye, and in this case, the retina of the giraffe. And what -- they found that there were specific specializations of the retina that seemed to allow them to have a high acuity, and they also found some very distinct and different architectural patterns in the retina of the elephant that were different from what they knew about other animals. And they still have to figure out exactly what that means. So this was also quite interesting to them.

So the point is, is that they're doing these neuro-chemical and anatomical architectural studies with some very important reasons behind them. And they can find very unique features about these animals that also might tell us something about how all these animals interrelate together, and also relate to the world.

So this is another one from that group and what this shows is that this is the dentate gyrus, which of course is in the hippocampus, and this is looking at the hippocampus stain for doublecortin in, I think this is 20 different species. And this to me is really amazing, because if you look at this, no two of them look the same. They all have very distinct patterns, which is really amazing. I can't really read these at this point in here, but I know there's like two different types of wildebeest in here; I think it's this one and this one, although I'm not 100 percent sure because I can't really see. But even those two are different. So this is really amazing that they've done this work and found out this information. And also the fact that these are all immuno-reactive for doublecortin and some other things that they've look at also indicates that all these animals have the potential for adult neurogenesis.

Okay, so I think, you know, what I showed there were a few examples. I mean, everybody knows there's elephants and giraffes in Africa, but there's also numerous other animals, such as like the panel I last showed you, which is also, you know, a very important focus that we need to keep our eyes on in Africa. Now the other thing that I wanted to mention is that in Africa there are numerous medical plants, and they've been used for years by tribal doctors and many people in Africa, but at this point there's been some, but we still don't know; there's been very little systematic study about what these different plants do. And you know, as I wrote on this slide, the world needs to discover their properties. It's important.

And I just put up a couple of slides of a woman that I know. This is just to give you an example of some of the work that's being done. It's Elisabeth Ngo Bum from Cameroon. And she's been studying this for years, many years. And she's looking at numerous different plants, and what effects they have on different diseases or problems that pertain to human beings. So this one is just an example where she was looking at the effects of this particular plant. Again, I -- chrysocephalum -- and she was looking at the effect in this case on pain. And then just the next one is another study where she and her group were looking at the effects of four different other plants. And in this case they were looking at the effect of seizure activity. So this particular category of experiment is something that's very unique to Africa, and really needs us to work on it. But these are some absolutely wonderful things that occur in research in Africa.

Now before I go on -- I think I have a few more minutes -- what I want to say is that there are a number of really excellent research institutes in Africa, really, really outstanding. And I just put up three here, just because I happen to know them. And they are the Instituto Nacional du Research Biomedical, the INRB in Kinshasa, Conga -- I think Desire Tshala-Katumbay mentioned that the other day, and it might have been mentioned other times -- the Noguchi Institute, which is in Ghana, and the Institute of Primate Research in Nairobi, Kenya. So I just -- they do research with animals, and I just mention these as, you know, a few that are really outstanding and that do really good work.

However, if we look at --again, we look at Africa, you know, and the size of it, there are many countries where there's really excellent work going on. And I also just want to point out South Africa, which I think is a little bit usual, and is -- on

the positive side, and as there's really some very good work going on there, and I'm sure you all know that. And so I think that's a little bit of a different category than many of the other places in Africa.

There's also -- and a few other places; I think Morocco also has some very good work going on, and several other places. But if we think about now, okay, what are the concerns? What do we need to think about when we think about animal research in Africa? So I said, there's many countries and some have some really good strengths and some have some problems. So I want to go over a couple of those.

So one of things is, despite these really wonderful number of species, much of the work that goes on in Africa is using the familiar rat species, or mouse species -- I probably should have put in that there. So there -- I mean, on the scale of things, there's limited work in the number of species that are available in Africa. Another thing that really interferes with animal work in some cases is that the electricity is not stable. And there's not good water available. So what that means is that very many different types of experiments can't be done. I mean, this is obviously true for any type of research, but it's a serious problem with animal research as well.

Animal care is quite variable, and in many instances, or I don't know, maybe even almost all countries outside of South Africa, I think that the researchers have to take care of the animals themselves. And what that means, there's a different level of care. So a person or a group of researchers may be given a room to house their animals and people have to take care of themselves, and what that means is that some people take excellent care of their animals and some people don't take such excellent care. So, the kind of odors and the level cleanliness is quite variable even within the same room.

So, another thing is in some countries there's no way to dispose of animals. So if you do an experiment and the animal is basically dead at the end, what do you do? And honestly, I don't know. This was just explained to me as a problem, but you know, I'm not, I'm not sure of what happens to the animals. In most countries outside of South Africa the idea of ethical approval is not insisted upon. Now, that doesn't mean that it doesn't happen, or that the animals are treated badly, but it's just not a factor that enters in to research in many countries and for many people.

So, another thing is that there's -- now, in other instances some of these animals are looked at, the animal models are established, but there are few tools for continued sophisticated analysis. Like if you take a unique animal, but you're not able to do genotyping on it because you just don't have the equipment. It's just not available. Another thing is -- and this one is really important, and this one is -- I'll put up at the end where I really hope that -- so, this just went black. Does this mean something? That -- does that mean that I have to stop or -- I don't know.

Anyway, okay. This here -- anyway. So, what -- let's see. The expertise is lacking. So, yeah, so what this means is, like, even for the types of experiments that we may think do not require a lot of fancy equipment or a lot of money, like behavioral type experiments or immunohistochemistry, people are not able to do them because they just don't know about the experiments. They don't know how to do them. They haven't been exposed, okay? And this is another instance where I think the Fogarty could be really instrumental and really great in helping to ameliorate this problem.

There's poor communication between departments and poor institutes, and -- between departments and institutes, and I've heard this a number of times: that there could be some kind of very nice piece of equipment in one department or in one institute, but there's no communication with other people in trying to figure out how they can share, how they can work together.

Okay. So, this is just another example. I'm not going to go through this, but this is from James Olopade in Nigeria, and he's been able to find a number of different features about this African giant rat. So, he's been able to work on this. He's been able to find out a lot about the architecture, about the fact that adult neurogenesis looks here and some other things, but most of this he was not able to do in Nigeria. You know, he had to share this work with somebody else so it could be carried out and they could find out these specific things. The other thing is that we could really use some kind of procedure for breeding these animals. In this case, for every rat that they used they went out and caught it. And it would be really useful to establish some kind of breeding programs for these particular animals.

Okay. So, let's -- so, those are some of the concerns. So, let's just look at Latin America for a second. Now, Latin

America, again, is similar to Africa in some ways. There's some countries were there's really absolutely fantastic research going on -- Brazil, Uruguay, Argentina, Chile; I mean there's some really wonderful things going on there, but there are other countries which it is lacking in really the kind of research that we would hope would go on there, someday. But I wanted to just point out that over the last couple of years, again, IBRO has been able to help to organize some kinds of programs that can help to harmonize some of the research throughout Latin America.

And this is a group of people who undertook some of this organization. This is Pedro Maldonado, this Silvina Diaz, and this is Ana Silva. Those are the only ones I know of this group. But they have been really working hard to get people together to actually harmonize the type of research regulations that's going on throughout Latin America, and this is just their -- and so they've come up with this program where, you know -- again, I don't have time to go through it all -- but where they can really coordinate throughout Latin America a systematic look at regulations about doing animal research, and also human research.

So, this is my last slide, and I just put out a couple of challenges in that, you know -- and I think this is -- these are some reasons or places where the Fogarty has done tremendous good already, and hopefully can continue to do that in establishing communication between departments and between countries. This is something that Desire Tshala-Katumbay mentioned in his lecture, is that, you know, there needs to be a way that people can talk to each other and bring information back and forth, and promote mechanisms of sharing techniques and resources, because even where they exist they're not shared a lot of times. I mean, I know that a lot of this obvious, but also to promote the value, intrinsically, of animal research.

And I just put down these four examples of some really, really interesting animal models. So, where people have begun to study them, but there's still so much to know, which is not really being worked on that much. So, this is a naked mole rat, which does not get cancer, and be exposed to severe levels of hypoxia and does really well. The spiny Egyptian rat where there's a picture here, and this guy can regenerate skin injuries. Nobody has actually looked at the central nervous system to see what's going on there. The laughing hyena, which is exposed to very -- all fetuses are exposed to extremely high testosterone levels, yet the females have some of these male characteristics, but

they're still mothers. And the vervet monkey, which also has some very interesting properties in communication.

So, that's basically my last slide, and I guess, you know, we can discuss this more hopefully in a few minutes, and then we'll go on to our next speaker, Vivienne. I'm not sure how to work this.

[applause]

Thank you. It's just sort of…

South Africa: Animals in Stress and Development Research

Vivienne Russell:
Well, thank you very much, Sharon. It's going. Okay. Thank you. Thanks very much. First of all, I'd like to thank NIH and Fogarty International, and especially Kathy for inviting me, and also for providing the R21. You can't hear? Okay. Sorry. So, to repeat the thanks. I want to thank [laughs] I really want to thank NIH, Fogarty International, and especially Kathy for awarding the R21 and RO1 grants to Michael Zigmond, our PR, on a collaborative project. And without Michael we would not have done any of the work that I'm going to mention briefly to you today.

And so, the main outcome apart from the research, which I'll mention, is capacity building. And to begin with, another advantage is that it brought Willie Daniels and myself together. The three of us, Michael Zigmond at the University of Pittsburgh worked together with me at the University of Cape Town, and Willie Daniels who was then at the University of Stellenbosch, and it was very useful to work together and discuss a proposals and project, because being at the tip of Africa you don't get a chance to talk to other scientists about the work that you do. Very often you dream up your own projects and you're on your own. So, this is an amazing opportunity.

Willie subsequently moved to the University of Kwazulu-Natal, and there he set up a vibrant research group. He has several MSc and Ph.D. students, and in fact, I'm already working at the University of Kwazulu-Natal; I'm now working for Willie. And so the research that has been established is continuing mainly at the University of Kwazulu-Natal where, as I say, there's a large group of students who are benefitting from the research which he is continuing.

Okay. So, our focus was on development.

[inaudible commentary]

That's okay, thanks. Thank you. In looking a developmental stress, and it's -- our focus was on looking at the effects of stress on survival of dopamine neurons in a rat model for Parkinson's disease. And our very first study brought us together. It was a Ph.D. student, Ilsa Pinar [spelled phonetically] in Willie Daniel's lab, and she did her basic laboratory work at the University of Cape Town, and then did analysis of some of the behavioral data at the University of Stellenbosch, and then graduated with a Ph.D. at the University of Stellenbosch.

And she basically showed that postnatal stress, mild repeated stress of the removing the dam from the litter for three hours per day affected the animals in such a way that when they were subsequently exposed to the neurotoxins, 6-hydroxydopamine injected into the striatum, the stressed animals showed a greater loss of dopamine terminals in the striatum. She did behavioral studies as well. So, this is an example. The blue graph shows you the control, and this is measuring the number of steps taken within a period of time. The black graphs are the unimpaired limbs. So, these animals are unilaterally lesioned, and so the limb on the opposite side is impaired.

And here you can see the animals that had been subjected to maternal separation, the ones -- the bar in red, shows a far greater effect, a far greater decrease in the number of steps taken in a specified time. So, then the motor activity is impaired. And they also showed that the tyrosine hydroxylase staining in the striatum, it's decreased to about 50 percent in the non-separated animals, and this early intervention of maternal separation increased the loss of tyrosine hydroxylase.

So, this work was continued by Musa Mabandla, who is a Ph.D. student in my lab, and he showed that exercise was beneficial, that -- he was injecting the 6-hydroxydopamine in the medial forebrain bundle into adult rats at 60 days of age, and he was allowing these animals to exercise in running wheels that were attached to the cage; so, it was voluntary exercise. And he did various experiments where he showed that exercise reduced the toxic effect of 6-hydroxydopamine. And here's an example. In the blue graph is the non-separated animal, and these short -- he measured step length. So, the normal step length is here,

about 53 millimeters, and the impaired limb the step length was increased and exercise reduced the step length. So -- and there are many other tests that they performed to show that the behavioral impairment was improved in animals who were able to exercise.

Here on the left you see the animals all in red, rather the animals who were stressed, did not benefit from the effect of exercise to the same extent. You can see the red graph, the animals that are exercising; the step length did not decrease to the same degree. So, here we were seeing an interaction between the stress experienced early in life and the beneficial effects of exercise being diminished.

He also showed that exercise reduced the loss of dopamine neurons when it's expressed as a percentage of the non-lesion side, and when he looked at the actual counts he found that -- we were very disappointed, in fact, amazed to discover that there was no improvement in the lesioned hemisphere. The exercise did not increase survival of the dopamine neurons; instead the exercise decreased the tyrosine hydroxylase expressing neurons in the contralateral side. This was the first evidence of the plasticity of the brain, and the adaptation of the brain to the loss of dopamine neurons down-regulating dopamine function in the contralateral hemisphere.

And we spent a lot of time investigating the mechanisms. We're going into details. He used other prenatal stress model and got similar results. Looking at the mechanisms, we show that exercise increased phosphorylation of ERK. We and many others show that exercise increased the growth factor, b, d, and f, and the phosphor ERK is in this pathway, which leads to phosphorylation of CREB and gene transcription. And if you look here you can't really see the red bars. That is the absence of effective exercise on stimulating this pathway in the animals that had been subjected to maternal separation.

And we published that in 2012, and a few months ago this work was referenced as being the first example of an interaction like this between stress and exercise, and the authors repeated -- well, used a different strategy, they used treadmill running. And they showed that treadmill running similarly increased phosphorylation not only in this pathway, but also in the GSK-3 mTOR pathway. And they showed that immobilization stress impaired phosphorylation, and decreased b, d, and f, decreased signaling through this pathway.

So, we feel that we've identified that pathway, which is being affected by this early developmental stress, and it's being altered in a way that prevents exercise from having its beneficial effect. So, the result of this work is better understanding of what the mechanisms are, because we're trying to understand if we can pinpoint what the problems are, can we maybe address treatment to reverse it.

And again, the collaborators are listed here. Many students, and of course, the PI on these projects, Michael Zigmond at the University of Pittsburgh, and Amanda Smith, who worked with Michael, was hugely helpful. Some of our students visited Michael's lab in Pittsburgh and learned the basic techniques. The University of Kwazulu-Natal is where this research is being continued with Musa Mabandla, my student who graduated, who's now working with Willie. He's a lecturer in the Department of Physiology. And the University of Stellenbosch, we don't have anybody there any more, so [laughs] they've moved on; and the University of Cape Town, the neuroscience research is continuing. Yeah. I'm an emeritus professor there now, so I don't know how long I'm going to be able to work [laughs]. Thank you very much. Thank you.

[applause]

Reinaldo Oria:
Okay. So, I would like first to thank Michael, Kathy Michels for having me here, and the Fogarty International Center to have given so, so much support to our group in Brazil. So, I would like just to point out some of our findings based on two grants received from the Fogarty International Center. I also would like call attention about importance of building capacity in developing countries. And you're talking about animal models and some of our data come from studies performance in Fortaleza, Brazil, but this is basis also in a long term collaborative work between the Federal University of Ceara and the Center for Global Health at University of Virginia. So, it's also built on trust and long-term collaborations with key personnel, and people come and go in establishing new collaborations. So, very pleased to have Dr. Guerrant here, our PI, and I'm talking also on behalf of Dr. Aldo Lima, Fortaleza, Brazil.

So, as been previously talked by Dr. Guerrant here, we concentrate our work on the lasting and very striking effects of malnutrition [unintelligible] diseases early in life that could cause an important decrement in growth, also in fitness and cognitive impairment, reaching about 10 I.Q. point or lower --

decreasing to -- from 10 I.Q. points; and also causing poor school performance in children. And we have a series of work just showing this and confirmed this long-term impact to early child development.

These effects could actually double the global [unintelligible] for diarrhea, and it's really not yet well understood and this work has actually nurtured novel ways to understand how malnutrition can actually have a profound effect in lifespan not only in the very first years of life, but extending to 10, 12 years later. And now we are actually understanding more about the impact of malnutrition, and cardiovascular, and other neurodegenerative diseases later in life.

So, this is a very important vicious cycle that we have of diarrhea and malnutrition, and of course we need to find out new ways to break this vicious cycle when we look for causality and actually, because of APOE has been linked to Alzheimer's disease, we thought initially that APOE could actually have a role during early brain development. Just very few studies at that time actually studied APOE during early development. And interesting, what we found was the opposite of what we were expecting in the beginning.

We found that APOE was actually protective against diarrhea, APOE4 that was the early associated with Alzheimer's disease. It was protective, and you can see this by -- when you start [unintelligible] of diarrhea, but also studying animal models. So, it was a very interesting finding that we may think that while APOE4 by increasing cholesterol is protective for several aspects of early brain development, but maybe also indicates a problem later on that may increase risk for neurodegenerative disease and cardiovascular risk later on.

So, because of novel collaborations with people in Duke, Duke University, Dr. Michael Vitek, we could actually have studies with APOE4 [unintelligible] transgenic mice. Since mouse APOE gene does not have -- is not polymorphic, so the advantage of doing studies with these [unintelligible] mice could actually have better way to understand how APOE4 could be important during not only brain development, but also intestinal development. We actually found when we challenged these mice with under-nutrition and also cryptosporidium infection, one of the leading protozoa causing chronic diarrhea in children, we found that APOE4 was really protective not only growth, but also on the burden of infection, reducing [unintelligible] setting and improving histology, intestinal histology.

And then, we established because of this grant new, important collaboration. One of them is with Dr. Kipnis, Dr. John Kipnis at University of Virginia, and we are trying to understand better this cat [spelled phonetically] brain access, and see how much of impact during early development and disruption intestinal barrier could actually affect brain in a different way, different perspective that have never understood before. One of this is, wow, what is the changings in the intestinal barrier front can cause to the cat blood, bacteria translocation, and how sequelating LPS [spelled phonetically] could cause a kind of brain inflammation.

And interesting that reason on this we found that animals affected with cryptosporidium actually show more N1 macrophages [unintelligible] N1 macrophage activation. So, it's really now we are continue this, it stated, now established an understanding novel mechanisms that could explain better this cat brain access.

But also, regarding cardiovascular disease, we see that using our new approaches of metabolomics we found that animals infected with cryptosporidium actually have more TMA, and this was converted to TMAO, showing that, well, maybe because of this we can find a mechanism explaining how infection early in life and malnutrition could predispose children to atherosclerosis and cardiovascular disease with likely an important effect of APOE.

So, I would like to thank very much, and just to highlight the importance of capacity building locally. Because of the grants we could establish a new laboratory that focuses on APOE neurobiology, and of course the importance of inspiring new neuroscientist locally at our site. Thank you very much.

[applause]

Sharon Juliano:
Okay. So, Kathy, how much time is left?

Kathleen Michels:
We have a few minutes.

Sharon Juliano:
A few minutes. So, I guess we ask the other discussants if they have some points they would like to make.

Rodolfo Goya:
Well, I could just offer an insider overview of the animal situation, research animal situation in Argentina, which I know. There we have the option of purchasing our research animals from facilities that are owned by the universities -- they are not commercial facilities like here -- or we can raise our own animals. Usually we choose the second, because it's less expensive. We have in the major universities an animal welfare committee, and we have to submit our projects, grant projects and thesis plans, for example, to that committee for approval.

So, anyway, the cost of keeping animals is much lower than here in America -- I mean in the U.K., because probably the animal rights movement is much less active in Argentina. So, we keep our animals in good condition, good health conditions, but at a much lower cost. This gives us a competitive advantage to do, for example, aging research. We keep our animals, we age our animals, and so that means it's much less expensive than purchasing them when they are old.

So, this is generating -- well, I am biochemist by training, but really have an imprinting of physiologist, and for me, we do gene therapy. And in this kind of work it's just imperative to use animals; in vitro work maybe just a transient, intermediate step, but definitely you need to -- we need to use animals. I have a colleague that have changed the Latin expression "in vino veritas" by "in vivo veritas"; that is he will only believes in what finally has been proved in vivo. So, this is [unintelligible] my comment.

Sharon Juliano:
Thank you. Fleur?

Fleur Howells:
So, the main component I'd like to accentuate, or whatever, is that the value of animal models may also be misrepresented and not fully understood across Africa, and how they can be used if you don't have a clinical population; and also the translation between the different animal models and human disease; and also the cost-benefit analysis is also poorly misunderstood by many countries, because of the research ethics is often lacking. And this is just from exposure I've had when I've been at African conferences.

And then also, within South Africa, we are a bit of a different breed of African countries. So the research is far more extensive and far more established, thanks to people like

Professor Russell, who has had a long history in South Africa. And also, very important funding bodies such as IBRO, which is the International Brain Research Organization, has done immense capacity building across Africa, and through being an alumni with them, it's the introduction to the NIH, the introduction to Kathleen at the first SFN that I went to. And the opportunities that IBRO has provided, which also then branches with Prof. Juliano.

And with those opportunities is also included being able to go to, like Marine Biological Laboratory, and I participated as a student in the neural systems and behavior. And just knowing what was out there and how invigorating it actually, you know, science can be, because there are limitations within the developing world, and it was definitely motivating and exciting to be able to get exposed and go to different conferences and courses.

Sharon Juliano:
So, Fleur, I wonder if you could expand a little bit on a couple of the points you made, because I wasn't exactly sure what you were getting at. I mean, you said the cost-benefit ratio, and then something about not completely understanding the animal models. Yeah, can you expand on that a little bit?

Fleur Howells:
Okay. For an example is for -- to determine ethics in research using an animal model you need to ensure that the cost is less than the benefit. Cost to the animal and the benefit -- the bottom line is that we need to enhance human research, and if an animal model can provide that information to enhance the human disorder then it is of value and should be pursued. However, if you have an animal -- you create an animal model, which we understand the neurophysiology of, we understand the underlying mechanisms, it can be seen -- it is pointless in many respects, and that message is not necessarily carried out across Africa, I believe.

Sharon Juliano:
Okay. So, I think we have some time for questions, a few questions.

[inaudible commentary]

What?

[inaudible commentary]

Two questions, okay. Michael?

Male Speaker:
Yeah. I'd like to come out of the closet, I --

[laughter]

-- with a public confession is that I'm a rat runner by training, and I just love the work that's being done by those on this audience. I want to congratulate you. Just one quick question. I spent years running rats and looking at complex models of choice within concurrent choice procedures, and optimizing reward, minimizing pain, and when we added neurotoxic exposures, even very low grade, we found that it was really those complex choice models in minimization, maximization that were the most sensitive to those effects. Are you aware of any kind of work of that sort using, you know, choice procedures and operant conditioning models?

Fleur Howell:
No, not aware of those in experiments of that nature, but it sounds to me like you are lesioning the dopamine system, which is very much involved in choice and motivation. And it makes sense, but I don't know anybody who's followed that up.

Sharon Juliano:
Okay. Yes?

Male Speaker:
So, I find this session very interesting. We've listened to a great deal of discussion over the last two days of diseases, nutrition issues, toxic starch issues with cassava, almost none of which I hear is well represented in well-designed animal models targeted to either learn basic mechanisms, or to target treatment of people who suffer from these various maladies, not to mention all the zoonoses that we're also concerned with.

Are we missing an opportunity? I've done some animal research over many years, so I'm feeling old enough to say, I don't think a lot of it is that difficult at all. And just as in treating people medically, the parts that technically aren't available would be the sorts of things that Fogarty and other institutes could focus on in terms of building capacity when, as you've just eloquently stated, it's worth the costs. I'd love to hear people's further opinion on this, because it seems underrepresented here.

Sharon Juliano:
I'll just say two words. I'm absolutely agree with you 100 percent, and I think -- I mean, and I would say that Fogarty has done some of this already, so it's just -- I'm not exactly sure why there hasn't been a little bit more animal research here, but I think -- so that Fogarty is involved in this, as far as I know, but I think, absolutely I think this is really important, and if we could convince places like the Fogarty to pay a little bit more attention to these types of animal models that may be very useful. I think that would be absolutely fantastic, yes.

Vivienne Russell:
I have a very --

Sharon Juliano:
Let Viv say something. Yeah?

Vivienne Russell:
Thank you very much. Yes, I was very excited to hear the talk about malnutrition and the effect that these individuals display ADHD-like behavior, and also very excited to hear the work on APOE and malnutrition and diarrhea, because of the hypothesis, which is just an a hypothesis that needs to be tested and properly tested in animals, that ADHD, for example, is a result of an adaptation. And the malnutrition would give rise to an adaptation to a low, less than adequate food supply, which would down-regulate.

The brain is the most expensive organ in the body. It uses, I think, 25 percent of the energy, the glucose production, and so at times of food scarcity, if our blood glucose goes down below three we lose consciousness. So, it's an adaptation to reduce the energy requirement of the brain, but then the downside is the long-term effect of that reduced energy functioning of the brain. And I think that can definitely be tested in animal models, and it seems to cut across a few areas.

Sharon Juliano:
Yeah. Well, I think almost all of these -- I mean, many of the things we've heard over the past couple days could be tested on animal models. So, yes.

Female Speaker:
I know that you're running late; I just want to say one word. That is, the colleague of mine at the University of Florida, Greg Gray, just received a D43 for One Health. So, he's doing -

- he's working it from the College of Public and Health Professions with veterinary medicine in Mongolia. So, the One Health program is very important to these things that we're just mentioning.

Sharon Juliano:
Thank you. Okay. I don't -- Kathy, can we have one more?

Kathleen Michels:
This -- huh?

Sharon Juliano:
One more?

Female Speaker:
Yeah. That session is very important. Thank you very much for take the space for that. I'm Patricia Cardana-Gomes [spelled phonetically] from University [unintelligible] Colombia. With the support of the Fogarty R21 and RO1, we have strained [spelled phonetically] the facilities in Colombia. One of them is the vivarium, the first SPF, but a species pathogens free vivarium, and had permit the develop of the studies in gene therapy, pharmacological studies in Alzheimer's models and several [unintelligible] model. In Colombia, the university have invest in the growing of vivarium for support is by America research. Then, I think it's important to know that in Colombia there are importance force with the support of Fogarty, too. Thank you.

Sharon Juliano:
Thank you very much for letting that out. That's great. Okay. I don't know --

Female Speaker:
We have time or…? Okay. One more, and then we have to break.

Female Speaker:
I would like to thank the speakers for this particular session, but I would like to make a comment. The reason we do animal -- oh, I'm supposed to say who I am. Yuan Liu from NINDS. My comment is, the reason we do animal research is we use animal as models to study mechanism of diseases. There are two challenges, so far, because a lot of the animal models research, when we try to translate in to developing human drugs or therapeutics, we fail.

The challenges are two: one is some of the animal models only mimic the phenotype, not the really genetic model or the cause, or the real cause of the disease; for example epilepsy. If you throw a lot of drugs, you could generate seizure, whether that's the phenotype -- whether that's the cause mechanism of that particular seizure, we don't know. The second thing is a lot of the animal model research in the past was not being repeated or replicated in other models or in other laboratories, and so our institute now recently put a lot of effort in research rigor. So I'd like to make this comment too. We also publish a paper on research rigor. How can we make the animal model research more rigorous that we can translate in to human research?

Sharon Juliano:
Thank you for that comment. I think that's very important, and something we all need to keep in mind, but you know, I would also like to say that, you know, some of the animal models in Africa are so unusual -- you know, like those four ones I pointed out at the end -- that it -- you know, this naked mole rat who can survive hypoxia, I mean, and does not get cancer.

You know, I might be very useful for us to understand these mechanisms, and use them to understand better human diseases. And all those animals had something very specific about them that if we were to make use of the resources in -- and not only Africa, but throughout the world where we have these unusual animals that are so understudied, I think it would be very useful to science in general. So, that's my comment about that, although I agree with what Yuan said.

Kathleen Michels:
Okay. One more comment and then we want to let you all break.

Rodolfo Goya:
Very brief addition. We got in a naked mole rat. It is a really a very wonderful model, and also it's a wonderful model and intriguing for aging. The life expectancy of a normal rat is three years. The mole rat lives 25 years and reproduces; there is no menopause to that animal, apparently. So, it's quite interesting, and it is being studied in gerontological studies here in the State. So, animal models may offer real a lot of insight.

Kathleen Michels:
Thank you very much for a fascinating session, and obviously an example of the vistas that this program, and certainly animal research can open. So, thank you to the panel. And so, we'll

have a break and reconvene, and start again at 4:00 with the Research Capacity Building session.

[break]

Plenary: Research Capity Building - Creating a Pipeline: Lessons from the Brain and D43 Programs

Female Speaker:
Welcome, everybody, to the afternoon session on Research Capacity Building. We're going to be starting now, and Dr. Yaun Liu of the NINDS will be moderating, and Dr. Linda Cottler will be the chair. So, thank you very much. So, Yuan?

Male Speaker:
We have a SNAFU. This is out. They have to go by that.

VII. PLENARY: RESEARCH CAPACITY BUILDING- CREATING A PIPELINE: LESSONS FROM THE BRAIN AND D43 PROGRAMS

Yaun Liu:
Good afternoon. We're standing between dinner and the snow. All right. Very good. So, I represent one of the NIH institutes. The full name of our institute is National Institute of Neurological Disorder and Stroke. I just want to show you very quickly our contribution to the brain and the D43 programs. This is a fantastic program, gave us the opportunity to support global health in such a scale we never could do on our own, and we're so glad to collaborate with Fogarty and other sister institutes and centers.

So, in the past 10 years, the NINDS supported 20 R21s and 10 RO1s, and plus two D43s. So, you can see from this slide, what's the supported research areas. One, the highest one is epilepsy, and the second, next to it is HIV, and you heard from our mental health colleague today; and then we have all kinds of research distributed all over the place, because our mission is to support more than 600 different type of neurological disorders, but we really care about those diseases is more prominent in your area.

Can I have the next slide, please? I have to do it myself? What's it say? Enter here? Very good. Yeah. It works. So, in the past 10 years we also support researching 18 different countries, and you can see the largest majority, or half of it is in sub-Sahara, Africa. And then we have a lot of grants in

Latin America. Then we have some in South Asia and East Asia, and one in North America. We are very pleased and proud that 10 of the speakers selected by the program review committee came to this symposium are from our grantees. Some of them -- most of them receive grant, or the D43 grants, and one of the keynote speakers, although his brain program was supported by NIHS, but he got a key award [spelled phonetically], and many of them received multiple grants. So, I want to thank all of you, not only supported by NINDS, but all of the investigator and your collaborators for your hard work to demonstrate here today.

My next job is to introduce our speakers. We have three speakers and quite a few panelists for this session. So, I'm going to do -- introduce them all together at this point to save time. Our chair is from Florida University? Sorry, I apologize. University of Florida. Her name is Linda Cottler, and she's a full professor there. And then we have three speakers. One is Nancy Carney with his colleague Juan Puyana. Did I pronounce your name correctly? They are from Oregon Health Sciences University, but I believe your collaborator is from a different organization, correct, Nancy? Or is the same --

Nancy Carney:
Juan Carlos?

Yuan Liu:
Yeah.

Nancy Carney:
University of Pittsburgh.

Yuan Liu:
Right. Right. Exactly. And then we have Dr. Purohit. He is from the Mount Sinai in the Department of Pathology. He has been there working for many years, and contributes to the Brain Bank there. And I forgot to mention Nancy's work mainly is in brain injury, and she has been working in Latin America, and teaching and conducting research for over 13 years.

Then our third speaker is Joseph Zunt. Dr. Zunt is a professor in the Department of Neurology and Global Health, and an adjunct professor in the Department of Medicine Epidemiology at the University of Washington. He is very impressive. He gave me a list of all the brain-related or Fogarty-related grants he had in the past 15 years -- 15 plus years. He got eight awards from us, and started with a FIRCA [spelled phonetically], and then

was an NINDS-K23 training, then followed by R21, R01 in multiple areas. And his research has expanded from infectious diseases all the way to chronic disease in Latin America.

So we also have discussion panels. We have Michael Zigmond. Dr. Zigmond, just raise your hand so people know who you are. Bahr Weiss -- yes, very good. And Richard Scheffler. All right, very good. And Kerim Munir. All right. Please come up. We'll find a chair for you. And the -- another one is Dr. Kamal -- very good -- from Pakistan. And then we have Byron Good. Excellent. We have Ghada El-Hajj--

Ghada El-HajjFuleihan:
Fuleihan.

Yuan Liu:
-- Fuleihan, [laughs], from Lebanon. We also have Eric Caine from China.

Female Speaker:
We don't.

Yuan Liu:
No? Okay. Very good. So let's start.

Linda Cottler:
Hi. I'm Linda Cottler from the University of Florida, and I just want to say a few brief words. I have worked with many of the people here on this panel through the D43 mechanism, or I've been on review panels with these people, or I've seen their posters, and the work that they do is wonderful. I want to thank the Fogarty International Center. I want to thank Kathy Michels for all the dedication and hard work that she's done. I want to thank all the institutes for all the support that they give.

We started our D43 back in 2001 when I was at Washington University in St. Louis. We work with India, and in that time, we trained 15 people long-term about 17 months apiece. They went back to Bangalore and started their own laboratories there, and they're now -- it's a pyramid effect -- they're now training their own people in their own laboratories. Based on that, I cored [spelled phonetically] a program, which sun-setted a couple of years ago. We then submitted a non-communicable disease and a D43, and here we took the work that we had done to build capacity in Bangalore at the National Institute of Mental Health and Neurosciences to the northeast India where the need

is very great for building capacity, where the suicide rate is number one in India.

So I think -- just to open this up, I think that Lyndon Johnson, from 1968 when he started this program, to John Fogarty, the wonderful congressperson from Rhode Island, would be very proud of what's going on here, because the whole thing was started to build capacity, and that's what we're doing right now. So thank you very much for still being here at this late hour, and let's start with the first speaker.

Missing Pieces in the Pipeline

Nancy Carney:
Thank you. The last couple of days, we have heard a tremendous number of stories about really unbelievable accomplishments in the Fogarty programs, but if you remember, yesterday morning opened in the morning session with a question by Dr. Birbeck, which was what about the failures? What about the gap between the results that we're producing and actually causing change? So that is what we are here to talk to you about, is what is missing, not necessarily what is working.

I have the privilege of having worked with two groups in Latin America, who actually have been very successful in returning to their countries and creating for themselves independent, free-standing research programs that are self-sustaining. So they've been -- they and I have been in conversation in -- during the last couple of years about, you know, what is needed in the home countries that could actually empower the local researchers to be able to cause change in their communities. And I'd like my teams to stand up. The group from Argentina, and the group from Columbia -- Goose, Sylvia [spelled phonetically], please stand, say hello. These are the people who have trained me over the last 15 years in working -- [laughs]

[applause]

-- in the developing world. And as you know, our work is all in traumatic brain injury.

So in 2011, we started the conversation at a Fogarty networking meeting, what is missing? And the Argentina group led a kind of a sequestered meeting where only the international people got together, and they talked about what doesn't work in their home environment. So out of that, what we did is the Argentina group put on to their website a survey and we surveyed 96 programs.

We ended up getting about a 30 percent response rate, so this may not be completely representative. But what we -- the point was we were looking for, you know, from the horse's mouth what is happening out there.

And just briefly, what we found is not a surprise: lack of qualified statisticians, lack of equipment, poor relationship with Ministry of Health, lack of public sources of funding, and problems with money management that were, you know, distracting. So we said, "Okay. What is missing? What can we put in place in the Fogarty curriculum that might cause change in this area?" And what we came up with is leadership, that what's missing in our curriculum is, actually concentrate on developing our trainees as leaders, as community leaders, so that when they return to their communities, they -- in the face of no agreement and no authority, they can actually produce change.

Now, it's one thing to say, you know, let's develop leaders, and it's another thing to actually do that. Many of us in this room have been in leadership programs, and you know, more or less they're so-so. We're -- we were really looking for something transformational, something that didn't just teach how to be a leader, but the actual being on the court, being a leader in challenging conditions.

So what we are proposing is to, in the context of some already organized research training program, for example, perhaps a D43, to implement specific leadership training from the bottom up and the top down, so that when the trainees are done they are not only skilled as researchers, but they are skilled in how to cause change in their communities. That is our proposal. Now, I'm going to turn it over to Juan Carlos to talk about the particular approach we are recommending.

Juan Puyana:
Thank you, Nancy. You may wonder, what is a trauma surgeon doing here at a brain symposium? And what I'm going to do over the last four or five minutes is tell you how I ended up here, and why it is so important. I used to whine and be very unhappy about the fact that all the global health funding goes to infectious disease and neurologists, and we as trauma surgeons have done a lousy job in getting money for us, even though trauma kills more people than AIDS, malaria, and tuberculosis altogether. So I decided to change the context. I decided not to complain anymore, and that's why I'm here. I'm not complaining.

[laughter]

We're going to teach. We're going to give the tools to our students in these D43 to actually change their context. That's number one. Number two, we're now going to teach them leadership. They can read about Kennedy and Mandela and Gandhi in many, many books. That is not what we're teaching here. I want you, each and every one of you, to wonder in your own field where there is a lack of leadership. An easy way to say that is, come on, look at a newspaper. But I'm not going to make it that easy. Look at what you do in your field and realize that what you are are only half of what you could do if you actually used these principles.

So the idea is that our students will become leaders as a natural self-expression. It's easy to talk about these two neuroscientists, because at the end, what I want you to go back is look at your brain, and what is it about your brain that it stands in between you and becoming a leader is? And there's a lot of things about your brain that tells you things that sort of constrain your ability to be a leader. So I don't have to teach neuroscientists about that. The brain works on a past-derived future. We want these students to change that. A new future, and I showed that in a slide yesterday. The only way to predict the future is to create a new future, but not the same future better, not the same future with more papers or more publications, not the same future with a promotion -- no. A future that is different, a created future, and to do that, you need to get rid of those constraints, and that's what we teach in this course.

So what we need really are leaders that can lead in any situation, without or with any given authority, with or without any decision allocated, rights to make decisions, with or without any designated followers, with or without any special characteristics. Most people become leaders being totally ordinary people. Once they are leaders, that's a different thing, but you don't need to be extraordinary to become a leader. And finally, to be leaders in circumstances where no one agrees on what is the right thing to do. So if we actually put this into a program, I think we can make a difference.

Finally, the three basic components of these -- and I don't think I need to convince you of these. The reason you are sitting here is because you probably accomplished that -- is that leadership cannot happen without integrity, without authenticity, and without being committed to something bigger

than yourself. What is integrity? Your word, when you give it. What is authenticity? Not able to recognize that you failed giving your word. And three, committed to bigger than yourself is each in what you're doing with your programs is not just about your career.

In fact, it shouldn't be just about your own research. It should be about creating a new future, so that when these students actually finish what they're doing, Dr. Glass is going to say, "What were they smoking?" Remember what he said? The morning. What are they smoking? That's what we want them to do -- to create a whole new context and a whole new future. If you're interested about what this course is all about, I can tell you where to find it in the website. Thank you.

[applause]

Direct and Indirect Impacts of Research Collaboration: Cognitive Loss, India

Female Speaker:
We'll wait for the questions until the very end.

Dushyant Purohit:
Is my [unintelligible] on?

Female Speaker:
No, it doesn't come on yet. You'll have to [inaudible] over there.

Dushyant Purohit:
Oh. We just heard the synthesis of the pipeline and how fix that. I am going to tell you about -- with all those leaky pieces still, we can do something in the developing countries. My project in India brought me to this topic that -- in that I will discuss direct -- the direct impact of research collaboration. And the research collaboration -- yeah. This is the research collaboration. We studied develop research facility and studied dementia in Mumbai, India, with Mount Sinai and Nile Hospital [spelled phonetically] collaboration with additional partnership with KM Hospital [spelled phonetically] and Sinai Hospital. Mumbai, they join with us later.

The research development collaborators are listed under -- on the right side is -- the left side are from Mumbai, and these are the investigators and main -- our senior staff. And in addition to that, we have several other staff we work with. And

they got training in dementia studies. Only a couple of them had previous exposure to dementia, and now there is much productivity anticipated from this. And from Mount Sinai, there are groups of my associates who joined me in this venture.

Now, with that experience, I will tell you what the collaboration can lead to. So collaboration is -- the basic tenants are that in the -- it is at the heart of the operative strategies in business and industry enterprises, and in research. It brings together different skills and strengths, and leads to the success of the venture, and more can be accomplished faster and with less cost than by the involved parties working to develop it individually.

Now, take -- collaboration capability of any venture depends on the culture and structure of the collaborating partners, and how is their interest and commitment for the project? And this is what it is. Culture is -- I'll give you just one example of culture and structure. In any developing countries -- and there, that is also in India, bureaucracy really are, for whatever reason, they are not -- they are unhelpful in some instances, to some degree. Not totally; only the real need to push and to get your -- get what you want to do on your project. And that is one example I'm giving you.

And the partners also are like that; that they do not have exposure to what research is, what are the deadlines, what are the priorities. And that that -- their willingness to learn and held together is what is important. And collaborating technology use is another aspect of that, and everybody, every partner in the collaboration needs to understand that.

What are the direct and indirect impacts of collaboration on international research and development? Now it is the heart of our question, our interest, is that how it helped -- helps the Brain Disorders in Developing Countries Program. This is a different kind of collaboration. It is not an exact partnership of filling each of those needs or each of those skills -- lack of skill. It is something -- what we transfer, the knowledge, skill, onto -- from developed countries, or HICs, into developing countries.

Impact of -- now what are the impacts of HIC and LMIC collaboration? The collaboration brings together those research communities of -- and they develop a long-term, sustained, and meaningful partnership. And they are -- their productivity is a result of researching a lot, and that results in research and

development, and progress. That would not have happened without that collaboration.

Now, impact of this is establishment of research facilities in the low and middle income countries from -- for advances research, and training of scientists in the lower and middle income countries in advanced research matters. And generates -- it generates research funding -- findings to confirm the existence or extent of health problem studies in the research project, and that leads to actions by healthcare establishments, and thus elevating the -- alerting research [spelled phonetically] and promoting better health.

Collaboration fosters changes in the culture. Now, as I mentioned earlier, that they are not yet geared to the priorities of research, how quickly it should be made, how carefully it should be made. That is, after learning a year or two or three, that is in a -- people who are not initiated as a researcher can develop, and many of our staff, research staff was aware -- had little exposure to research culture.

Now, global health discoveries about aspect of this is that are prevalent in the lower -- low and middle income countries are important for high income countries as well, because of transmigration. People go from here to India, as an example, and from India come over here. So this is -- has broken the boundaries. So all this is, which are there can be here. So that is another aspect our program impacts on.

Now finally, the Fogarty Initiative Program establishes research capability in the low and middle income [unintelligible] to target it in this project, and without the Fogarty Program, cadres of new scientists in those countries would not be identified, inspired, trained, and then the -- they would perpetuate the research activity. The new scientists continue their enrollment in medical research, leading to a long-term impact on healthcare and distance [spelled phonetically] elevation.

Now, briefly I will tell you what our project has led to. Collaboration developed -- we developed this collaboration in developing memory clinic and Brain Bank research laboratory, and introduced -- am I running over? Sorry? It doesn’t work.

So impact of -- yes. The collaboration-developed infrastructure that was nonexistent about dementia research, and in that institute research was at a lower priority, and we really

developed the research area of our interest and that gives an example of what we can do there. They -- we introduced a structured clinical service and research in -- on dementia, and that was the first clinic-based program in the country. Before that, several epidemiological studies were done there, but a research similar to what we do in Alzheimer's research center in Mount Sinai, we have adopted, we adopted the same methodology there. Cultural -- then we also conducted clinical and pathological research studies on basis of those clinical works.

We trained a cadre of young scientists. There are about seven or eight scientists. They have continued working, three of them, abroad, and four or five of them are still locally working on dementia studies. And they're running a clinic and -- or helping in the clinic. We published work in both clinical work and pathologic studies, and a pathology study demonstrated that there is a -- Alzheimer's disease can be similar in extent as in New York [spelled phonetically]. Clinical work paper demonstrates or shows how the structure of medical investigation can be done.

Now, this is the example of what ATED [spelled phonetically] -- this battery [spelled phonetically] and all that were adapted from our Mount Sinai ADRC. And they all developed, and the researchers were trained in that. And this is pathology result. Impact of Mount Sinai that -- all the work showed a need of further research in risk factors of Alzheimer's -- dementia, Alzheimer's disease and dementia.

And one good example is that a resident that is a student in pathology had a topic of -- on the same topic, a thesis written for his M.D., and he was very successful on that, and he presented the same work in a conference, the national conference, and he won the first prize on that. So that slide -- accomplishment can be achieved by -- in spite of [spelled phonetically] the researchers.

Successful, wide-ranging community outreach is another thing. We had several -- two senior centers roped in in our work, and they provided cases, as well as controls. And we also developed a relationship with industry -- industrial people, and they are committed to any fund we require after we start another project from the NIH. We have also seminars, we conducted seminars for medical -- for doctors and nurses, and other people who became now more familiar with dementia.

Now, this is the end of it. The -- what -- this is the message of it. It says, collaboration is the basic tool for sharing Fogarty Program's goal for research development and capacity building in the lower and middle income country. So collaboration is -- can be productive. There are also same problems as it is -- there are in any venture. So some successes, some disappointments, but again, one should not -- stop thinking of disappointment and continue working. Thank you.

[applause]

Research and Research Capacity Building for Neuroinfectious Diseases

Joseph Zunt:
Good afternoon. I'm Joe Zunt from Seattle, and first off, I'd like to thank Dr. Michels from Fogarty Center and Drs. Liu and Wong [spelled phonetically] from NINDS for supporting me over many years; and also Sylvia Montano [spelled phonetically], who without her help, none of this would have been possible. I used to say she's my Peruvian wife and then she corrected me, "No, actually, you're my Peruvian" -- or she should be my Peruvian sister. So, my Peruvian sister.

So I was asked to talk more about some of the barriers that we've been faced with, rather than focus on our research accomplishments, but I just have a few slides to talk about research to put it in focus. And it looks like this went out of order. So we -- I think our largest project is encephalitis in Peru, and before we started this project, there really wasn't any existing laboratory capacity for diagnosing encephalitis. So currently, we now have 774 patients enrolled. I'm not going to go into the results, but we started with zero, and now you can see the patients we've enrolled across the country. And this continues to expand. And so it's been a great success, I think, because of the need that we identified earlier on, which I'll get into.

This is -- unfortunately my Mac died on me, and it threw some of my slides out of order. But I wanted to mention, as far as the research barriers, some of you are new to the whole brain disorder, some of you have been battling the same issues that we have for years: money transfer, IRBs, the necessary evils -- or I shouldn't say evils, but necessary barriers that are, at times, insurmountable, but very important for keeping everything going. I'm not going to focus on those. What I do want to

focus on is some other types of barriers that we've been overcoming, and one of them that continues to be mentioned is the pipeline. So how do you get this pipeline of young investigators to eventually take over once you're too aged, which may be coming up soon for many of us?

So we first started off with a survey of neurologists, which many of you have noted is really the way you want to start. I mean, assess what is needed. We are really lucky in Peru to have 254 neurologists. So, many other countries may have one or none. So we had a survey of neurologists across Peru saying, well, what have they taught you in medical school? What have they taught you as a resident? What do you want to know? What do you need to know? And I don't know if you can read some of these, but a lot of them wanted to know methodology, and a lot of them wanted to know, how do you write a grant? So we decided to address those issues.

So this really went out of order. I'll jump now to building capacity. So one thing I wanted to mention as well was, how to get to the point of building capacity. One of the ideas that we had in mind that was ingrained from my mentor, King Holmes [spelled phonetically] in Seattle, was to really seek out synergies. So we have had a lot of luck with synergies. One example was that San Marcos, you can see in the bottom -- I'm left-handed, so I'm going to screw up my sides too, so sides and slides -- bottom left-hand corner is how the laboratory used to look. So really, nothing. And we were lucky to have a group called ICOS Corporation in Seattle go under, and they approached King and said, "You know, we've got all this equipment. Do you want it?" And the group from Kenya and the group from Peru, namely me, jumped up and said, "We'll take it." And then Kenya said, "It's too expensive to ship it, so you can have all of it, Joe in Peru." So we shipped a large container full of equipment to Peru, and once the director of the Tropical Medicine Institute heard of that, he said, "Well, you know what? You can have the entire floor to build a research lab."

And then they -- we started with the renovations, and we went to our Center for AIDS Research and said, "We're trying to build this but we need gas, we need water," and then they gave us little amounts of money to push forward. So I -- there was one speaker this morning who talked about receiving $70,000 -- I think the guy who was in with Charm [spelled phonetically] in Costa Rica. But approaching your directorship of your university is, I think -- it can't hurt. They can only say no, right? But sometimes they'll say yes, and that's what we were

fortunate to get. So we also received money to put in this generator. We also have a vaulted stabilizer. So now we have in the middle and up above a very functioning lab where they're now branching off not only diagnosing herpes by PCR, but moving into molecular characterization of syphilis strains in Peru. So it really builds capacity in a way that we certainly hadn't imagined when we first started off.

So I have no idea what the next slide is going to be. Okay. So, training Peruvian neurologists. This is where, I think, I had the most fun, and Sylvia I think as well, and this has been an evolution. So it started off with me going to the Neurologic Institutes and asking, when I was there with my seven-month-old son and wife in 1996, "Do you have a neurologist I can collaborate with?" And the director took five seconds and he said -- actually, he got on the phone and said, "Sylvia" -- and she used to have crazy hair back then. He said, "Sylvia, is your hair combed?" And that was in Spanish, and --

[laughter]

-- said, "Get down here to the office." So that's when I met Sylvia, and it's been a history since.

But we found that through our collaborations, we make all these other collaborations with neurologists, and they see who? They see students, they see residents, they see fellows, and they say, "You know, this person here looks fantastic. You should train them." And that has been, I think, the key to our success. By talking to our collaborators, being open to training, we've identified all of these people.

And I think this is where it's been tricky, too, to figure out how to best train people who may not be bilingual. So we have kind of a hodgepodge of opportunities, some in Peru where they can do an MPH, some they come to Seattle and we'll train them for a few months to see what their caliber is and if they look great, we may do what we call a sandwich program. So we'll have them come up to Seattle for a year of MPH, go back to Peru, do a thesis project, and then come back, finish up their MPH, and then go back to Peru. So the sandwich is the training on either side. That's the bread. The meat is the thesis project.

So these are people that we trained, and we still are in collaboration with, I think, all of them, and many of them have risen to positions where they've become even more wonderful a collaborator. So third from the top, Erin McKespie [spelled

phonetically], is now the director of the Neurologic Institute, the only Neurologic Institute in Peru. Carlos Abanto [spelled phonetically] is now the director, or the president of the Stroke Association in Peru. So they're also saying, you know, this resident looks great. Send them to Joe and Sylvia.

So, responsible conduct of research -- this was supposed to be earlier on. So we started off with the R21 knowing that this was a need, going out and offering these -- what turned out to be really fun events. We had some simulation patients, we invited people from NIH to come down, we invited people from OHRP, which was fantastic, because OHRP is who gives out the FWAs -- so alphabet soup, but federal-wide assurance, which you need in every country if you're going to receive NIH money and do research. So by bringing OHRP down there, they met a lot of colleagues, and at one of the conferences in 2007, we had 11 representatives from other Latin American countries come together and talk about how they can build a continent-wide collaboration. So that was very productive.

So now, jumping ahead to the future, what are we going to do next? So this is something that I don't know if any of you have worked with me out to Rizack [spelled phonetically], who is another program officer, but he's also been a wonderful help. He asked me, "Well, what are you going to do next now that you've got things running smoothly?" And what we've kind of naturally progressed into is virtual education. So, I mean, we can't go down and -- nor do we want to go down and teach workshops. It ought to be something that becomes owned by our collaborators, and then becomes arborealized [spelled phonetically] south, south collaboration. So we started with this corner upper left, nothing, and went down to this virtual classroom, and now we're able to do synchronous and asynchronous teaching, we're able to use Redcap, and our hope is that now that we have an 80-point bridge in Seattle that they'll be able to have distance education virtually across the country, and eventually to other countries as well.

I did want to point out another part of the synergy, getting the Global Health Fellows Program grant. Chandy John [spelled phonetically] is one of the other co-PIs on this. This has been a fantastic collaboration for us to expand to other areas of the world. Through the Global Health Fellows Program, they've just started this new program called the Clayton-Dedonder Mentorship Fellows, and what this has now branched out into, in addition to the virtual training, is who's your next generation of mentors? So this is similar to leadership. Who's going to train your

next generation? Who's going to train your mentors? I was never tapped on the shoulder and said, you know, you're a mentor now. I never received any training. It was just luck that I had a fantastic mentor who I learned by emulation.

So this is more an intent to evaluate the mentor training capacity within institutions -- we're actually in three countries. I'll just focus on Peru -- but then bring tools that are so homegrown so that they can develop their own mentor training programs, and hopefully those will be institutionalized for generations of trainees that won't necessarily be related to what we're doing.

This is actually preceding what we are doing, the mentor training. I'm almost done. This is actually one of the assessments as well. So what do mentors want? What was surprising for me is that they don't really want remuneration. They don't want us to give money. They just want recognition, and they want some kind of resources to help them become better mentors. And steps towards institutionalizing mentor training, I think this is a challenge for many of us who work bi-nationally. I use Skype. Others use ooVoo. Others -- there's lots of other ways that you can use -- PolyCom -- to do distance mentoring. This is not only useful for us, who are off the continent, but those within the continent working rural to urban environments.

Now, I don't want to talk about that. I do want to mention another program we're starting with the Kuskaya. This is with Patty Garcia [spelled phonetically]. Behind her, this is another synergy. This is the School of Public Health being renovated, and fortunately King put in some funds to help put in this system on the second floor, which will be a site where all of our trainees can go and be housed. And I see you're nodding. This is hopefully something that's also spun off of the brain disorders, is looking at chronic diseases, namely stroke, across Peru. We're hoping to start that later. And that is it. Thank you. [laughs]

[applause]

Discussion: Panel of D43 and Brain Grantees

Linda Cottler:
Wow. Great mentoring mosaics we've heard here. Starting from the first speaker to the last speaker, it reminds me of when you're sitting in a waiting room, and you see those pictures

that are -- they have little captions underneath them. Leadership is action, not position. That reminds me of the first talk. And then all the way through synergism and the mentoring mosaics that we've talked about here, including training and responsible conduct, and integrity -- all the things that we've talked about tonight.

So why don't we now take -- each person on the panel will take 2.2 minutes and just give us an overview of the mentoring mosaics that they've used to really build capacity. Let's start with [inaudible].

Ghada El-HajjFuleihan:
So I'm with the American University of Beirut. We got our D43 in September 2012, so we are very junior in this experience. And building capacity for us at AUB was a composite of training the trainers and training the trainees. The opportunity, of course, is that NCD is the leading cause of death worldwide and the Middle East, and there is a huge gap in research in that area, and the D43 kind of came in to plant the seed to fill that gap.

The strengths that we -- we're having on our side is that, of course, AUB being a very strong institution, having a very good infrastructure, and a lot of support. The challenges, of course, are that there is limited ability to build research capacity outside our institution; the spectrum of needs is quite wide, so whatever we come up with had to be modular. And the obstacles are the cultural barriers to conduct research, modeling, and taking paradigms from the Western experience for building capacity in research.

The opportunities we had open to us was very strong collaborators in the U.S., the ability to make our training modular from short-term training, which is a limited summer training program for seven weeks with 12 credits in quantitative methods, directed to explore NCD's issues. Medium training went on to add to that a few months of additional research; and the long-term training is the Master's degree in clinical translational research.

We've graduated 20 summer trainees last summer. We have four of them, who did the medium intermediate training, three of which are here and have four wonderful posters, so I think the productivity has been amazing. And we have three master trainees right now. So we're trying by this modular approach, having the various sophisticated, in-depth training modules

available, address the variety of needs not only in Lebanon, but also in the region. I think the challenges are sustainability, funding, and long-term ability to absorb the capacity that we're building, because of course, there is a limited number of institutions that are going to absorb our trainees.

And I think the last thing that we're challenged with, which the trainees here kind of reflected on while we were discussing this outside, is what happens? Where do they go? They are trained early enough in their careers that they want to go to the States and get additional trainings. Would they come back? That's a big gamble. Do we want them to come back early when they're so junior and cannot build capacity so fast? And we're discussing, no, you should stay longer so you can come back and be the mentors to the future generation, and the role model. So I tried to really give you the mosaic of all the changes and opportunities we have, and all I've done is actually reflect on some of the wonderful points brought up by other speakers.

Linda Cottler:
That's wonderful. Thank you.

Kerim Munir:
Thank you. Again, thank you for Kathy and the Fogarty. I am Kerim Munir, and I'm based in Harvard Medical School and Children's Hospital. And we had a D43 beginning in 2001, like Linda, and we had it refunded. I would just say take a micro-view that the -- many of the principles that we followed really were what Fogarty had instilled, which is the idea that add-on evaluations were to partner with an in-country partner that was relevant. And we had a UNICEF work in -- with the earthquake in Turkey that we partnered with some other universities that were pre-existing, which were somewhat serendipitous.

And I remember very well talking to my mentor, Leon Eisenberg at Harvard, and asking him what I should do after the earthquake, and he basically said, "Those people here at Harvard will not do anything." Of course, he was using an expletive, but I will delete that --

Female Speaker:
[laughs]

Kerim Munir:
-- and you should go.

So based on that turning point, I think the Fogarty partnership for us was that there was this requirement of in-country capacity building, which is really not existing in any other NIH idea. And I think that many of the things that Fogarty does really does what Linda was saying in terms of the principle has been very successful, and I would urge that not much has changed. To use Santayana's quote that those who don't remember the past are condemned to repeat it, but we are sort of, as Fogarty PIs, D42 guys, we're condemned to remember our mistakes and to try to build upon that.

So what I would say that, we've had a very big -- we were the only training, research training program in Turkey they ever funded, and I think will ever be funded now since Turkey is regarded as a G20 country, but the biggest tribute came actually in 2012 when I read a letter, a very detailed letter, with my very esteemed colleague from Brazil, Louis Roday [spelled phonetically], who is a child psychiatrist also, like myself, based in Brazil, but has a lot of international work. And basically he said that Turkey and the Science of Index publications was the number one in all the lower, and middle and upper middle income countries in terms of publications.

So, well, that's not necessarily -- was our program, but I would say that what happened is that some catalytic emergence of activity that led to some resurgence, and some change that occurred that led to more publications, where, for example, when we were interested in doing the development of national meta [spelled phonetically] policy, people then became very engaged in that idea.

So overall, I think the process worked very well and I'm very thankful, and we hope that we'll continue to work in the region. Thank you.

Linda Cottler:
Thank you very much. Bahr?

Bahr Weiss:
I'm Bahr Weiss. I work in Cambodia with my colleagues, and Vietnam. We also have had a series of three D43s, and the first one -- it was a developmental grant -- and Kathy asked us how we'd accomplished so much with such a small grant. And my response was, we stay in cheap hotels --

Female Speaker:
[laughs]

Bart Weiss:
-- and she laughed and -- but that wasn't a joke. So one of the issues that I see is, it's how you use your funding, and you have to use it very efficiently, because even when you have a larger grant it's not a lot of money. So that's one thing I see for sustainability, is to always go into it at the very beginning with the knowledge that you have your very small amount of money, and use it wisely.

Another thing that we found that helped us develop the program was that we worked with Vietnamese Americans when we were working in Vietnam, and we will start working with Cambodian Americans, but they were very eager and glad to work on the program without any kind of pay, and just covering their expenses. So we were able to extend the program by working with Vietnamese Americans.

I think ultimately the most important thing is you need to focus on what the local needs are really, because I know that's something that's obvious and we all talk about, but it's pretty clear that that's not always the case, that a lot of times we go in with our own interests and it's hard to move that over. For instance, our current program in the developmental part of the -- our work, we also have had a brain disorder, and an unrelated RO1 -- was to develop a graduate program of clinical psychology. This was not really my idea. It was the dean of our school in Vietnam, and when she suggested this, my initial reaction was, I'm not really interested in doing a lot more teaching, because I have as much teaching as I want in the U.S.

But this was her idea. We thought about it, we talked with people, and we decided this was the best idea to sustainably develop infrastructure. So we went with that, and now the Master's program has been running for five years. It produces about 10 Master's level clinical psychologists who are trained in clinical work and research a year. The PhD program will start either this year or next year. And in Vietnam, you know you're successful when you start getting imitators and competitors, because when people see something that they think is successful, they do it if it fills a need. And we've seen that, so we know we're successful and that we filled a real need, because we have a lot of competitors.

In terms of the barriers, one of the things we've seen is that there is the obvious barriers, there's the lack of training, there's financial limitations, there's no infrastructure. We've

seen cultural barriers, because we're psychologists, primarily work with mental health from a psychological perspective, although we work with social workers, psychiatrists, et cetera. We run into a lot of cultural problems. One is that, for instance, grandparents are not really interested in their children being involved in these interventions, so we have to work around that.

Probably the biggest issues we've seen though are not the things like this that people talk about, but more things like destructive competition between LMIC and HIC researchers, both within and across those groups, and a lack of professional standards for conducting research. So the barriers we've seen are not the ones that people typically talk about or acknowledge, though when we talk with our colleagues they've run into the same things. Thank you.

Linda Cottler:
Thank you. Byron?

Byron Good:
I'm Byron Good. I'm a professor of medical anthropology in the Department of Global Health and Social Medicine at Harvard Medical School, and I also want to express my thanks to Kathy, but also to Enid Light [spelled phonetically] who's been a supporter for many years, and we had a T32 program over at NMIH, as well as through this -- through our program, which is a program I'm training -- a D43 program in China that -- which we've had for -- since 2001.

I want to take what Kathy instructed us, which is not focus on what we've done, but we really take the issue of what I think -- and I -- what Fogarty could do better in, and I want to say, number one, talking about what's missing is often very important. Fifteen years ago, Arthur Kleinman came in and pointed out that there was -- that there really should be a focus on mental health and on brain diseases. And 15 years ago, there was no such program at Fogarty, and I think that mattered. And a few years later, Paul Farmer and Jim Kim were very powerful in arguing that delivery should be more of a focus of attention than what it was, and I think that has also had an impact.

Now, I wasn't here yesterday, because I was introducing Paul Farmer to a group of medical students, but he simply pointed out that many of the students there were themselves basic researchers, a number of them would be involved in translation,

but pointed out that if that very often translation into -- and basic research and translational improvements have actually led to increasing inequalities, and he took the example that we all know that in the early years of ARVs that led to actually vast increase in inequality between poor and rich.

And so I want to ask the question, pipeline for what? And to simply say that I think we can do better in having a pipeline that focuses on delivery, and that focuses on more equitable delivery.

Now, I think Fogarty has precisely been committed to those kinds of issues because of its international quality, and I just want to say that I think the -- that putting implementation science onto the agenda was important, but is not enough. It's important and not enough, because first of all, it's often assumed that implementation science simply means delivering that which is evidence-based, and in many of the places where we work, what is evidence-based is not known.

The fact that yes, we know that any psychotic medication works, but much of what is known about how to deliver is -- there's this idea that you can simply translate from high research settings to low research settings, from a place where there is, you know, 100 times more psychiatrists than in Indonesia or China, and the question is, like translation -- so creating the basic models of what's evidence-based is, first of all, critical, and secondly, the assessment models -- we heard a very nice set of talks about instruments, et cetera -- are often also not available for doing the most basic outcome studies around these issues.

Now, I want to say that the problem is even larger than that. We're moving at a period of time in which the only way to prevent growing inequalities is to scale up delivery systems, and to figure out how to do that. I'll just say -- one or two moments. And there is something -- there is a failure of basic sciences around scaling up, I would say. I -- you know, we all know that the mechanisms for scaling up have to do with bureaucracies, and yet we know almost nothing about how to improve the quality of bureaucracies in the delivery of basic health services.

Jim Kim, who's been a big supporter of this, now head of the World Bank, came to Harvard to give a talk. I raised my hand and said, "Jim, you know, you talk about delivery, but what about basic studies of bureaucracies?" And Jim changed the

subject. And I say, like he's the director of the -- of, you know, one of the most inefficient bureaucracies in the world, and it's not a surprise that he doesn't want to really focus attention on bureaucracy.

But certainly, those of us who get involved in delivery, and saying the only way to make the findings from these kinds of programs that have been so fantastically described here, that will make them available in providing care, make them widely available requires that -- an increased attention to sciences associated with the delivery, and with scaling up of care. And so I think that's one area that I would put my finger on in saying we need additional work.

Linda Cottler:
Thank you very much. [inaudible]

Kati Phillips:
Hi, my name is Kati Phillips. I'm from the University of California Berkeley, School of Public Health. I'm here on behalf of Richard Scheffler. Our project is the socioeconomics of mental health services in southeastern Europe. We are fortunate enough to be in our second round of competitive renewal. This program has been running for 12 years now. We work with five countries in southeastern Europe, including Serbia, Albania, Moldova, Bulgaria, and Romania.

So the way that we conduct the program is we send out a request for proposals and then we work with a co-investigator, Razvan Chercheres, who is the director of the School of Public Health at Cluj -- Babeș-Bolyai University in Cluj-Napoca, Romania, and he actually used to be one of our trainees in the first renewal of our program. And he recruits the trainees from these five countries, we bring them to Berkeley, and we highly encourage cross-country collaboration. We focus on multi-disciplinary issues, including the healthcare workforce, stigma, access to mental health services, depression, and chronic disease. We assign faculty mentors to each research project, and the faculty mentors come from backgrounds of psychiatry, psychology, economics, sociology, and public health.

All of the countries currently in our program are low-income, high substance abuse regions with limited access to services, and high rates of stigma against these very prevalent disorders. Because of this, we focus on implementation science using policy and organizational implementation, and institutional models. We focus heavily on policy in these areas, and by -- how we do this

is we work with the health ministers and try to recruit the interests of key stakeholders in these regions.

We actually just had our training meeting last week. We brought about 18 trainees to Berkeley. And some of the issues that we also face are the cultural barriers. Some people in these areas are very reluctant to ask for help, which is something that we were not expecting. And an example of this is our co-investigator attempted to publish a paper three times and it was actually rejected all three times until he finally asked the faculty mentors for help in making the paper more grammatically correct in English. And after he did finally ask for help, it was accepted and published.

And in these 12 years, we have had 220 graduates from our program, several hundred papers and publications, and three books, one of which will be forthcoming from this round of funding, titled "Mental Health: From Communism Until Today." And Dr. Scheffler wanted to send a special thanks to Kathleen and the NIH, and Fogarty for allowing us to continue with this work. Thank you.

Ayeesha Kamal:
Thank you. I'm Ayeesha Kamal, Aga Khan University, Pakistan. We are a D43 grantee from 2009, and we do a lot of -- our work is enablation [spelled phonetically] of both for stroke and stroke research.

To give you a -- just a little idea of what we've done in this -- you know, we're babies compared to some of the 12-years-old, and whatnot -- is that when I applied for this grant, we had a stroke training program and a biostatistics program, but we had only one U.S.-trained stroke researcher, namely myself, when we applied. And now we have seven long-term people who are doing exactly the same thing, probably better than what I was trained in the States, up to 400-plus people who have been trained in workshops, and six projects that are being run now by the people that have been trained by the Fogarty and the NINDS program. So it's a huge change in, you know, in the culture of research from, you know, just training people to training thinking people, from people who were used to pedagogy to evidence-based thinkers, who appreciate research, who are asking questions.

And the fact is that, you know, this grant has led to spinoff grants. And so we were recently awarded a Grand Challenges, a Canada grant, and it's called Bold Ideas with Big Impact, and since we're doing technology development for things that have

emerged from the trainees of this program. So, you know, it begets -- research, it begets creativity. And so I think that's -- it's an amazing thing that's happened. And so I want to thank people that -- you know, that were a part of it and for enablation of the same.

I think the next thing I'd like to talk about is, where we go from here. We've heard today and the last two days this whole full circle of -- you know, I've seen all these babies being born and then they're not getting enough love and care, and then their brains are just not functioning. I mean, that's a theme that's being developed, and then they grow up and they have strokes and heart attacks. Well, each of us has to do something of our bit to sort of break this circle.

And you know, there's not -- there's a lot of appreciation for maternal and child care, and very little really goes to diseases, like strokes. Well, there's no point having healthy babies if the father is dead, and then they can't go to school, or the father has a stroke, and they can't go to school, and they have to take care of this child -- take care of this person. And so it -- you know, you have to somehow get into these points in the circle, and try to break the cycle of creating non-resilient societies, because your adults -- you know, an educated, working adult is a very important thing in a low and middle income country, and having them [inaudible] out by a stroke or a heart attack, or disabled permanently, is a horrible thing. It -- I don't think we quite appreciate or measure the impact it has on societies, and we re-get [spelled phonetically] these persons.

Now, getting these people in back is always going to be messy. It's always going to be collaborative, it's going to be complex, and we have to get used to the messiness of complex interventions. We have to know that we just -- it just can't be about me as a researcher. You know, at this point, my team contains biomedical engineers, it contains statisticians, it even contains media artists; it contains cartoonists who do 3D rendering for some of the education that we do. We need to have this feel of messiness if you're going to get this work done. And I mean, I -- and I don't think we completely appreciate that, even, I think, at a global level, we don't completely appreciate. We need to talk to all kinds of people now, and step out of our silos, or the way that we are thinking about this.

Interestingly, we can be much more messy in developing world societies. We talked about what's so special, we talked about environments and animals, but we didn't talk about the culture of growing societies. We have a word we call it in -- in Urdu, it's called 'juggaar' [spelled phonetically]. It means find a solution. You have to find a solution that works. That's how we think. And I think we need to take advantage of that innovative approach. You don't hear no. It's a society of figuring out where things are. And so the -- it's so much easier to have these interesting collaborations and people sitting across things, which we don't in developed world societies, I think because we've gotten very structured here.

How can we better some of the trainings and innovate our training further? I think that's -- one thing I've noticed is that, yeah, we started training neurologists, but now we're training nurses, we're training techs -- we're training anyone. Bioethicists, they want to come and have newer ethics [spelled phonetically] sessions with us. So we're training a wider variety of people than we ever thought we'd end up training.

I think long-distance training is something, you know, that you build on, and I think that will apply very well, even to a societies, such as ours where, you know, people who really want to work, but they can't step out of the house at that point in time would really benefit from long-distance training.

Something that we think would benefit our systems is standalone courses focused on developing certain modular skills that, you know, our trainees may lack; for instance, health economic analysis, or you know, certain special statistical methods, complex intervention methods. I think if there were -- you know, the NIH has this really nice online ethics course, for instance, which, you know, at least it gets a nice starting base to anyone who starts the program. So if we had these specialized skills standalone courses that would cut across all our training programs. I think that that would be something pretty amazing. It would be a networking issue, it would -- we would collaborate more, and we would build these individual skills where we really need these skills. I think that's all I'd like to say. Thank you.

Linda Cottler:
Thank you very much. You've all come a long way for this time, and I appreciate all that you have to offer. We'll be writing some of these things up that you said today in our manuscripts that we're going to be doing on the next two days. We're going

to have some writing circles. Well, what we've talked about today are the really principles of community engagement, transforming our culture at our own universities that are in our own towns and our own cities. It's really getting out of our silos, and really breaking down these barriers.

So I would like to -- I know we're not going to have time for questions. Do we have a few minutes for questions? Sure. Let's take some questions. If you'll please come to the microphone.

Male Speaker:
Yes. Thank you very much. I really like the section of the discussion, but I want to make a comment on something that I feel -- that I see very critical for a training program that can be designed these days to be sustainable. And I'm so pleased to see that -- I could feel the speakers that mentioned that. If you want -- I haven't been a grantee, a D43 grantee, but I've been on the field and doing training activity for so many years. There are some critical things.

The way you see the society changing now is that there are so many things coming out of unconventional ways of learning. People in the developing world now, they don't necessarily need to go to school to learn. You go to Africa, to the very poorest country, very remote area, you'll find cell phones, people go online, people can move from one area to another and learn without being in class.

Second, you also see, you know, any kind of self-directing learning processes going on. Irving [spelled phonetically] say that. To me, it's good to put an emphasis on the training or the content of the training program, but the critical thing is, who do you train, and what do you train in? Who do you train if you want the sustainable program to have an impact? You think next generation. I was also pleased when I heard Joe Zunt talking about. You think next generation.

The second thing that I want to emphasize that I was really, really, really pleased to hear about is that we think very little about leadership. It's key. You may have all the kind of knowledge that you want. Look at the experiences that we have had in -- with African countries. After the independence, the most -- the country that has the most trained people, trained in the Western hemisphere with the best degrees, those countries are the worst now to, the leadership issue.

Third aspect, when I heard about the Vietnamese program, when you have a training program without trust in relationship, when you don't have a program without people that can have their hearts in the society it's difficult to build anyway. I'm sure the Vietnamese program has been able to achieve certain things with little money, because they worked with people who were culturally competent. And you don't know to go -- you don't need to go to school to be culturally competent.

And if you look at all these different aspects, to summarize what I was trying to emphasize here, everything goes back to leadership. At any program in which there is no leadership and there are no clear, or this no clear matrix for leadership, it's -- these tend to failure. You'll provide knowledge to people, there are people to have -- they'll be able to develop some skills, they'll try to solve the problem, but it's got to be sustainable. But I'm very pleased with those initiatives, and I hope more can be done in the way that has been proposed by the first speaker and some of you to be more successful for the future. Thank you very much.

Male Speaker:
Well, there's the old statement that if you teach a person -- you give a person a fish, they eat for a day. You teach a person to fish, they eat for the rest of their lives. And I think one thing that Fogarty has done per penny is produced more fishermen around the world than -- and productive fishermen, unbelievably productive fishermen. The most concern is that there's no shortage of fish. There's plenty of questions, and there's plenty of people. What's the problem is, is the river to sustain the fish, and that's sustainability. And I'm mostly concerned about all of these wonderful trainees, and these legs up on publications and research strategies and questions need sustenance. And once we dry it up, or once we -- they exceed our ability to fund them, what happens?

We've seen certain hints. Some countries -- South Africa, India -- have national funding agencies to which you can apply. Joe has gotten into the university stream where he's gotten some help from the university. But these are sort of oddballs really in the international stage, because most people don't actually benefit from being [laughs] a university affiliate, and most countries don't have a national funding agency.

But my biggest fear is that we produce all these wonderful, bright-eyed people, and they can't sustain themselves. And I think this is a major problem, and I kind of wonder why there

isn't a World Bank person here telling us how to do this, or et cetera. The kind of imagination we've put into building this capacity needs to be applied to keeping these people sustained once they return to their own environment and they lose they leash of sort of E.U. and U.S. funding.

Male Speaker:
I just wanted to say something that I'm dying to say. There is a book called "Why Nations Fail," written by MIT economist Daron Acemoglu, and it's published last year. And I think he in that makes arguments about certain countries being -- having extractive institutions and extractive society, restrictive on democratic rights, and so on, and inclusive societies. And I think in the long run, as you know, the slogan for Bill Clinton '92 was "the economy is stupid," but the idea is that, how do you sustain economies, is going to be based on societies that are sort of more open. And I think that those sustainably question beyond individual and organizational levels at the institutional and governmental levels is going to be ultimately based on that.

I think that in some respects, the World Bank hasn't got it right. The idea, for example, of Thomas Freedman and others that modernization or cell phones will solve everything in societies that are very restrictive on people's rights is not necessarily correct, and I think Acemoglu makes that argument with some examples where, in the long run in societies where those kinds of things occurred, that the government failures led to regressions economically, and then regressions in some of the developments that occurred. And that might -- it's shown by Rosling's [spelled phonetically] work also in terms of the World War -- the effects of World War I, World War II, and effects of colonization in how things developed.

So I think these are very important questions that hopefully we -- I don't think Fogarty can answer that, but I think Fogarty has got the parameters absolutely right. Say, in my opinion, introducing the idea of collaboration, partnerships, and ethics, inclusionary ethics, and the issue of requirement for research capacity building, which is essentially what the committee is reviewing on. And I think those are fantastic, and that's why those fishermen are --

Female Speaker:
[laughs]

Male Speaker:

-- living productively.

Linda Cottler:
Quick.

[laughter]

Male Speaker:
I know we're running out of time. Thirty seconds. I just want to pick up on the messiness point. I mean, it's such a great point. You know, there's such a -- there is a tension and it's -- I hope people understand that I say this in a -- really with the best intentions -- that there is a tension in working in collaborative partnerships with partners in developing countries, because things are done differently and things work differently, and sometimes the people on the ground actually know how to negotiate and navigate those difficult kind of barriers, whether it means you've got to not tell Kathy and spend some money on a sheep for the local chief or -- [laughs] as a gift to pave the way. There aren't -- they aren't as messy -- you know, I shouldn't have said that. I never did that, [laughs].

But there's messiness, and there's -- and I think one of the things that I'd like to just say, and it certainly doesn't reflect my experience in this program at all, but I just am aware of it, that I think there's a potential for developing country partners to be potentially disadvantaged in terms of power relations, and not actually capacitated -- we talk about research capacity, but not capacitated to enter into those partnerships as equal partners. And so I think it would be really good for the program to also look at how to assist people to become equal partners, and make sure that those relationships are equitable and balanced. You know, that's what I want to say.

Female Speaker:
Hi. Just -- I will take 30 seconds.

Female Speaker:
[inaudible]

Ayeesha Kamal:
Yeah, I --

Female Speaker:
Oh, sorry.

Ayeesha Kamal:
Thank you for appreciating the messiness, and also appreciating that the solutions also arise from the ground. If you're listening, they're there. I mean, chance favors the one who is prepared to listen.

The other aspect that someone raised here was a concern for sustainability of funding, and you know, it's very interesting -- and I'm just sharing the view from Pakistan -- is that, you know, at least at our university, which has kind of set the -- sort of the culture for other universities, at least in medical research fields, anyone who is appointed a senior instructor has a -- is given a seed money grant through a granting processes and review to start getting initial data to then apply to the high education funding, which is considerably practical funds to do research by the government of Pakistan. And that's a program that is still going on.

Another interesting fact is that Pakistan is, I think, the fifth biggest philanthropic nation in the world, and at the moment, I'm seeing this really interesting shift of -- for philanthropy beyond, of course, dealing with what is the immediacy to NGO agencies, who are now putting money in research. And so there are these foundations that are coming up who want a research component, and will be funding, and are funding projects within Pakistan, which are relevant to the people, so that the people that you're producing are able to get chances not just internationally, but even nationally, especially in the beginning of the carriers where they need to get this data to make a compelling application.

Linda Cottler:
Ken.

Male Speaker:
Real briefly, Bob Zucker [spelled phonetically], who's not here, who was one of the first ICORDA [spelled phonetically] grantees too, at the first network meeting he said, "Success comes down to your collaborators," and I've remembered that over 12 or 13 years. The key thing that the last person was saying is about being equals is that comes down to us, the PIs. I try my best and so do my colleagues to treat everybody equally and as an equal partner, and you can ask them to the extent to which we've been successful. That comes down to us treating people as equals.

Kathleen Michels:
All right. Well, thank you. It's 5:00 --

Female Speaker:
One more [inaudible] --

Kathleen Michels:
All right. Just one more --

Female Speaker:
Just -- yeah.

Kathleen Michels:
-- because we have a few more things to --

Female Speaker:
-- very, very quickly.

Kathleen Michels:
Okay.

Female Speakers:
I'm Tatiana Scovsky from Penn. I'm actually Colombian birth raised, and now hoping to work with Columbia. And so I applaud all of you who brought in like the difficult questions. One of the things that Fogarty could do is just advise ministers of health or whatever in terms of sustainability how to use their money. I mean, in Colombia we're in a very weird situation right now where there actually is money and they're wasting it. I mean, I hate to say this, but like they just don't know like what they could do, like where there's research, how to do it, you know, and that could go a long way to sustaining research in our countries, is advice from NIH.

Female Speaker:
-- brief because we have a --

Female Speaker:
[inaudible] All right. Okay. I'd like to make a comment before -- so I think Fogarty has over the years done many, many different programs: the FIRCA, the Grip [spelled phonetically], and now we have the Brain Disorder, we have the D43 -- we have many different things. We usually come to a meeting. We enjoy the celebration, we learn from each other, but when we go home, we still in working in our own silo. So what I would like to encourage, what we have seen so much at this meeting is we -- at lunch, we have a group of people, we all work on epilepsy, but

in different countries and different projects, and I would really like to encourage us to stay in touch, really thinking about the common themes, and maybe we can encourage more south to south [spelled phonetically] collaboration, and an across institution collaboration, and brew some other collaboration among the people here.

This is very unusual. We have more than 400 people all here in Bethesda. It's not only to celebrate what we have achieved, but start new things. So I would like to encourage people to think about how do we build a community from these many years of investment, and -- yeah. Yeah. So actually we want to [inaudible] --

Kathleen Michels:
Okay, thank you everyone. I actually -- the energy around this is fabulous, and I'm sorry I was out of it for a little bit, because I was trying to figure out -- the whole day tomorrow was originally supposed to be about research capacity building and brainstorming for research capacity building and training, not just around brain disorders, but all chronic non-communicable diseases and the intersection with infectious diseases. As you know, we've been trying to figure out what we could do tomorrow. It's on at the Double Tree, Ballroom C, and we'll be starting at 9:30. So all of you who were interested in the energy around this, if you're still here tomorrow, please come. It might be a little tight, but we'll do it.

Also, if you have posters, probably best to take them down today. Originally, you could leave them up because we had the Natcher Building all day tomorrow, but if in all likelihood it's closed down, if a miracle happens and we come back here instead of going to -- then you can put those posters back up. But I would take them down today. And there's a lot of lost and found stuff that -- so when you go out, if you could check and see if you lost anything. So I --

Female Speaker:
-- there be a phone that we can call in in case we're snowed in, we can't drive --

Kathleen Michels:
You can call -- I'll give -- there's a number on the website, and I'll make sure that that gets to --

Male Speaker:
[inaudible]

Female Speaker:
Yeah, can you give us the --

Kathleen Michels:
Yep.

Female Speaker:
-- address?

Kathleen Michels:
The Double -- that's happening. That's totally happening.

Female Speaker:
No, no --

Kathleen Michels:
Oh.

Female Speaker:
Do we call [inaudible] --

Kathleen Michels:
Oh, we'll try -- we're going to try and set up a conference call number. All of this information will be on the meeting website, so we're going to put all this information up tonight.

So right now, I'd like to introduce Dr. Raj Kalaria, who will give a summary of the past couple of days. He's kindly offered, and he could do a much better job than I can. And I'd like just to thank all of you, and thank this wonderful panel. It's been a wonderful day, and I -- you know, I appreciate all the shout-outs that I've been getting, but you know, really this program is due in large part to the involvement, both intellectually as well as monetarily, of all of the institutes and centers, and the program officers that have been working with you all. So much appreciated, and Dr. Kalaria.

[applause]

VIII. Summary of the First Two Days: Future Directions

Raj Kalaria:
So, ladies and gentlemen, first of all, before I introduce and say anything about myself, I think we owe a very big thank you to Kathy Michels.

[applause]

And if Kathy's listening, in Swahili, we say, "Asante sana sana" [spelled phonetically], which basically means, from the heart, thank you very much.

So my connections with Fogarty go quite a long way -- 2002. In fact, Don [spelled phonetically] mentioned the history, but it was ena-blo [spelled phonetically] heavyweights who came to -- at the invitation of the NIH at the time, in 2002, to really debate about support -- NIH supporting the developing countries. And I think we had an interesting meeting. We went away with a sort of -- I'd kind of describe the glass half full and half empty. But then, of course, things developed from 2003, and here we are today.

I think everybody sitting now, and those who went home early because of the weather, et cetera, can feel that we've had an absolutely riveting, wonderful, in-depth, in-height, in-width, in-length kind of science. Would you all agree?

[applause]

And what the beauty is, is that a lot of this can be done with R21 grants.

[laughter]

What little money goes a long way, and as somebody described, we -- you know, cheap hotels, et cetera. So it's really good, and I think the vision that Fogarty had, along with the partners that were -- when we listened to yesterday, at least their leaders, just had the right idea to support this. Yes, we -- NIH cannot support -- give a lot of money to the world, I mean, because the interests really lie in the United States. But nonetheless, even a fraction has helped, and I think that's in all of our faces here and certainly in mine.

Now, I am -- have seen, and looked at perhaps some of the descriptions of, or a lot of the research that was presented here, and we've talked about sustainability. Meanwhile, what do we do beyond R21 and beyond RO1? We have to find -- we have to be innovative. We have been innovative already in terms of what we described in our research. We have become all sorts of people. We have become scientists, clinicians, clinicians saying that, you know, our patients can wait while we find a cure, or amuse them while we find a cure, [laughs]. And not

only that, but we have become teachers, mentors, we have become plumbers, electricians, negotiators, bankers of all sorts transferring money, and wheeler-dealers to get this research going in the developing countries. That's what I see when I just sat there listening to you all these past two days, and I think it's a wonderful thing.

The other thing is I think what we have appreciated is what James Whitworth said in a wonderful article in The Lancet in 2008 or so from the Welcome Trust. He said, "Research is not a luxury. It is a necessity in the low and middle income countries." So if we find a good a project, a project that's really worthwhile following, then follow it to the end. Follow your heart to it. And I think we've demonstrated that in these two days.

We've talked about policy makers. Well, hold public meetings, invite them to a little party, and you'll get perhaps a hearing ear. If you get even one hearing ear, it's just like all those donors. If you get just one donor to donate towards and become a partner in R21 or RO1 proposed studies, then that's worth it, isn't it? And we talked about stigma, well educating people. Go to church meetings. After the service, go and talk to the parishioners, and in that way, we kind of relieve the stigma of either -- whether it's epilepsy or anything. Are we spreading HIV in the community, for example, by our research? So we talk to them, see what we're doing. We invest in the community, because we perhaps pay someone to be the interviewers from the community. We tell them what we are doing, and I think pay back in the way, feedback our research -- that brings success. And that certainly has brought success in quite a bit of the work that I've done in -- largely in sub-Saharan Africa, in the Kenya, Uganda -- well, Kenya, Tanzania, South Africa, and now a lot in Nigeria, mostly following post-stroke survivors -- longitudinal studies.

And then we talked about I think access to services. Again, in a large number of developing countries, whatever the clinical problem, whether it's from birth onwards or to the other spectrum, families are there and they really look after the -- our patients, don't they? And in -- and services are lacking, but I think by education, the point that I made before, can come a long way in educating them and talking to and finding local incentives as well.

So I think we should try and think really -- and a good point was made earlier on. We should -- must think beyond R21 and

RO1s. Sustainability. In some way, be innovative. Let's just try to be innovative, [laughs], and find ways, and you know, be even neuro-politicians at times if we have to, especially.

So I think that I necessarily don't want to go into all the science, but I want to say something about IBRO, the International Brain Research Organization, and just a couple of words. I think it's already been mentioned very much, and I think the -- my particular privilege to serve in the executive committee of IBRO has -- is really gratifying, because a large number of the IBRO alumni from the schools are part of the Fogarty program, or have become trainees and now mentors, and I think that is commendable.

And the other, perhaps, point I will finally make is, may, as I talked to Dr. Glass yesterday, may the Fogarty International Center continue with this. I mean, they have to continue with this, isn't it? They've seen the success, 10 years, and I think more can be built up. I'm sure publications will come right, left, and center. There is no doubt about that at all, and capacity will be built, and is being built, and we can just build more to it, even perhaps with the lack of support of the despots that we have in certain countries, [laughs], who I think we spoke about those. And they're all together. They all should be put in one room and perhaps talk to each other, [laughs], you know? But this where we are. So the -- for the little -- what we receive from the Fogarty, I think makes a lot, is a large value and big money.

So let's, I think, again, really take our, as I think Dr. Chandy -- [laughs] John said, you know, "Let's take our hats off," not only to Kathleen, but to Fogarty and -- because it has absolutely changed the lives of all of us in some way. I think you'll all agree with that. If the Fogarty Brain Disorders [laughs] Program wasn't there, I don't think we would have really been where we are. Would you all agree? Yeah.

[applause]

And I think that in writing there's a lot of stories to be told, a lot of successful stories to be told, and the number of fellows and the number of individuals that has really been -- have been affected, and we've changed their lives. So I think wonderful success. So thank you very much, and as we say in Swahili, "Kwaheri kuona" [spelled phonetically]. It means, "See you again. Goodbye, and see you again." Thank you very much for all.

[applause]

IX. ADJOURN FOR THE DAY

Kathleen Michels:
Thank you, everybody, and I just want to -- my colleague, Dr. Maria Said, stand up, and Enid Light -- I don't know if Enid's in the audience -- have been communicating with you about the day tomorrow. They might not be able to make it -- probably won't be able to make it given the snowstorm and conditions. I will be, because I'm just going to hang out here and go over there. But anyway, I wanted to introduce both of them, because they've done an incredible job putting the agenda and communicating with everyone about tomorrow. So -- and they'll be participating hopefully by phone, so we'll keep this rolling.

So thank you, everyone. Thank you for all of your work. I mean, this is -- I mean, I -- again, I appreciate the shout outs to Fogarty, but it's really all of you. So give yourselves a hand, and thank you. I think we can adjourn.

[applause]

[end of transcript]