U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

INTERAGENCY AUTISM COORDINATING COMMITTEE MEETING

FRIDAY, NOVEMBER 22, 2002

The Interagency Autism Coordinating Committee [IACC] convened in Bethesda, Maryland, at the National Institutes of Health [NIH], 31 Center Drive, Building 31, C Wing, Sixth Floor, Conference Room 10 at 9:00a.m., Dr. Thomas Insel, Chair presiding.

PARTICIPANTS:

ELIAS ZERHOUNI, M.D., Director, National Institutes of Health [NIH]

THOMAS INSEL, M.D., Chair, *IACC*, Director, National Institute of Mental Health [NIMH]

DUANE ALEXANDER, M.D., Director, National Institute of Child Health and Human Development [NICHD]

MYRA ALFREDS, M.S.W., Comprehensive Comm. Mental Health Services Program

KATHRYN CARBONE, M.D., Food and Drug Administration [FDA]

JOSE CORDERO, M.D., M.P.H., Director, National Center on Birth Defects and Developmental Disabilities [CDC]

LISA FREUND, Ph.D., National Institute of Child Health and Human Development [NICHD]

HELEN TAGER-FLUSBERG, Ph.D., Boston University

SYBIL GOLDMAN, M.S.W., Senior Advisor on Children

LEE GROSSMAN, Autism Society of America, moderator

PARTICIPANTS [continued]:

DEBORAH HIRTZ, M.D., National Institute of Neurological Disorders and Stroke [NINDS]

ANNE HOLMES, Ed.D., Eden Services

GAIL HOULE, Ph.D., US Department of Education [Ed]

MERLE McPHERSON, M.D., Health Resources and Services Administration [HRSA]

DONNA NOYES, Ph.D., NY State of Department of Health

CATHY PRATT, Ph.D., Indiana Resource Center for Autism

PATRICIA RODIER, M.D., University of Rochester

BENEDETTO VITIELLO, M.D., National Institute of Mental Health [NIMH]

PROCEEDINGS:

Dr. Insel: Good morning and welcome to the Third Interagency Autism Coordinating Committee meeting. I am Tom Insel, the new Director of the NIMH and the Chair of the Committee. I have to say that this is a very exciting moment for me because it's my first real moment on the job. This is a little bit of trial-by-fire.

As many of you may know, there are a number of Institute Directorships that remain open, and I'm beginning to wonder whether this is the way each Director is selected.

[Laughter.]

In any case, this is particularly exciting for me because I have a real personal and passionate interest in autism, and it's a field that I have been involved in for many years myself as a researcher, so I'm excited to be able to start on a problem that I care deeply about. I'd like to begin the meeting by just doing a quick round of introductions. Jim, perhaps you could start.

[Introductions.]

Dr. Insel: Thank you very much. As shown on the program, Dr. Elias Zerhouni will be joining us as well. He is delayed and will be here later in the morning. He is not going to be able to be here for the first phase of the meeting, but does intend to be a part of this at some point in the morning. That reminds me to tell you that there is a bit of a structural problem today, a little scheduling problem, in that there's an emergency meeting that's been called of the Institute Directors by Dr. Zerhouni. It's actually not an emergency in the sense of anything urgent, but because our normal meetings that occur on Thursday morning have been rescheduled the last couple of weeks, and he felt it was important to get everybody together at one point before the end of the month. And that will happen at 10:00, and so a number of us, Dr. Alexander, Dr. Battey, and myself, will have to step out just before 10:00. We'll be back at about 11:30 and Dr. Nakamura has agreed to take over as Chair for that section of the meeting. In terms of other structural issues we need to think about before we start, I do want

to try to keep very much on schedule this morning, so I'll be a vigorous taskmaster in terms of keeping the clock. But I wanted to talk about a couple of things that we need to consider before we get on to the agenda. One is that it was agreed at the last meeting, as I understand that we have minutes that will be available on the website and that would be reviewed at the subsequent meeting. And so you should have received copies of the minutes from the May meeting, and I wanted to check to see whether there are additional comments or whether we can vote to accept those minutes as they exist.

Dr. Battey: I move to accept the minutes as written.

Voices: Second.

Dr. Insel: All in favor? [Show of hands.]

Dr. Insel: Anyone opposed? [No response.]

Dr. Insel: Okay, accepted. If there are no other issues to bring up before we start on the agenda, let me just ask if there is any need for anything else. [No response.]

Dr. Insel: Then let's go ahead and start on the first item of the agenda, which is Dr. Alexander's update on the Collaborative Programs of Excellence in Autism.

Dr. Alexander: I'm going to pick up where I left off at the May meeting. If you read the minutes, you'll remember what I talked about then, about the Collaborative Programs of Excellence in Autism, and provide you an update on what's happened since then. You will recall that this is a major program and a joint activity of the National Institute of Child Health and Human Development and the National Institute of Deafness and other Communicative Disorders.

We fund, starting in 1997, ten sites around the country, at that time as program project grants, that function together in terms of interactions, to do both site-specific research on autism and some joint activities in collaboration, focusing on the neurobiology and genetics of autism. These represent the major activity in autism from NICHD, and of $19 million expenditure on autism on 1002, about $10 million is devoted to

the CPEAs. When I spoke to you in May, we were in the midst of a recompetition of this group of sites. I can report to you now that of those ten sites, nine competed very well and have been funded after our September Council. One of these is funded by NIDCD, the others by NICHD. The one that did not succeed in successfully recompeting is expected to resubmit an application that will be reviewed. In the meantime, they are one that joined the Network one year late, so they still have funding and are still participating as part of the Network. So we have funded the continuation, the second phase, really of the Network. These sites continue their activities. In the ensuing five years, there will be a greater emphasis on Network joint activities that are made possible by the large number of subjects available for study from the collaborative nature of this activity, but there is also substantial funding provided for individual site-specific research. These also have been converted from the program project grant status in which they existed in the first five years, to what we call U-19, or

cooperative agreements, so that they are functioning now as a Network where there is greater staff participation from the two Institutes in joint activities with the Network, in addition to, again, the site-specific work that they do. This facilitates their functioning as a network. In addition to that, we also have activities with this group to enhance their functioning as a Network. The whole group meets once a year. They will be meeting in May as a steering committee, presenting research results from each of their programs, and, again, working on joint projects. In addition to this annual meeting, there are monthly telephone conference calls among the principal investigators with the staff from the two Institutes, giving progress reports. And there are several subcommittees of the Network that have their own activities by conference call at regular intervals. You will be hearing from two of the principal investigators from this Network later this morning. Several of the major activities of the Network that are going on at the present time include genetic studies.

The Network has been able to investigate the follow-up to the report that the homeovox A-1 gene was associated with autism, by following a larger number and studying a larger of individuals with autism, 250, compared to the initial small study. And in this larger study, there was no evidence of an association of this gene with autism.

They're currently looking at other possible genes of interest related to autism, the Realin gene, the WIN- 2 gene on Chromosome 7, the serotonin transporter gene, and abnormalities on Chromosome 15Q-11. There's also a sibling linkage study that's led by the investigators teamed at the University of Washington, collaborating with four of the other CPEA sites, looking at multiplex families. These are families with at least one child with autism and at least one unaffected sibling, looking at phenotype assessments and genome scans for autism susceptibility. A major activity and, I think a major contribution from this Network is the work on a common measures protocol. This is an effort to develop a common diagnostic, behavioral, medical, and neuroimaging

evaluation of children with a presumptive diagnosis of autism. The protocol is very comprehensive, and this selection of common measures and standardized administration of these measures across the Network is a major undertaking that is going to facilitate and make more important and significant, all future Network projects, as well as benefitting the whole field of autism. Just a couple of weeks ago, there was a report in the literature in the Journal of Child and Adolescent Psychiatry from a study from two sites in the Network, the University of Washington and the University of Colorado, looking at serotonin as a purported treatment for autism that improves some of the behavioral symptoms of the children. We have supported previous studies that have not shown such an association, as has been initially claimed in the literature. This particular study looked at 86 children who have clear diagnosis of autism, and compared administration of secretin from standard pork, a pig source, from a human synthetics secretin, compared to placebo. And the three groups showed

absolutely no difference in this randomized, double-blind, controlled study in any of the performance measures that were looked at. So we hope that this will be the last secretin study that we have to do.

Finally, let me mention the data coordinating center. When I spoke to you in May, I mentioned that one of the things that we were planning to do to facilitate Network activities was establish a data coordinating center to help with cooperative studies in different sites across the Network, as well as serve as a central repository for data from the collaborative studies. We have moved ahead with this. It was on a different schedule from the recompetition of the Network itself. The RFA was published last summer. Applications are due next week, and they will be reviewed in the spring and taken to our Council in June for funding in July. We're reviewing this in anticipation that this data coordinating center will be able to serve both the CPEA Network and the new STAART Center, so we hope that we will be able to get a facility that will have the

capability of serving both, and have one data coordinating center for both the CPEAs and the STAART Networks. So that's where we are. Thanks.

Dr. Insel: Thank you.

Dr. Battey: I'd just make one comment on that. I think Duane should be congratulated. The formation of this Network is what allowed him to rapidly go in and look at the secretin problem when it was raised as an issue. Really, without a network like this, and without the sort of cooperative agreement mechanism, you can't move with anything like the nimbleness that the Child Health Institute was able to do to quickly get an answer to the secretin issue when it was raised, and I think that's very important in this field.

Dr. Insel: Other comments or questions, clarifications? [No response.]

Mr. Grossman: Duane, at that meeting in May, that has all the CPEA centers, that annual meeting, is that open to whomever?

Dr. Alexander: These, in the past, have been meetings just of the investigators for presentations.

Voice: Usually we do a day and a half or two days open to the public.

Dr. Alexander: Did you hear that?

Mr. Grossman: That's good. I have a question about the funding for these centers. If you could just go into that a little bit more, is the funding going to be expanded as the research expands?

Dr. Alexander: These have built-in increases in their budgets. They are really only on the order of the standard increase that we have for non-competing renewals of about three percent a year escalation. So they have that built in. If protocols are developed that require augmentation, there is the potential for supplementary funding for those as a Network, but that will depend on just what is developed from the Network. It would have to be provided above and beyond the built-in three percent per year increases.

Dr. Insel: To follow up on that question, you had mentioned that there had been -- that nine were re-funded. Was there an additional one that

hadn't been funded in the first round, or is the whole set now nine centers?

Dr. Alexander: One of the ones that was funded in the first round did not receive a fundable score in the recompetition. That was one where we did the first-round funding in two separate years, so this one has a year yet to run. We anticipate that the investigator will take into account, the reviewers' comments and submit a revised application. That will be reviewed to determine whether that particular site will continue as part of the Network or, if not, they may come in with just a regular program, project, or an RO1 to continue their work.

Dr. Insel: Thank you. Are there other questions or comments? [No response.]

Dr. Insel: If not, let's move along to the report which is on the Studies to Advance Autism Research and Treatment. These are the STAART Centers, and Deborah Hirtz will be doing that report.

Dr. Hirtz: Good morning. I just have a few slides, and I was going to review for those who

were not here last time or who may not recall. The STAART Centers were established according to the stipulations of the Children's Health Act, and the plan is to have a network that consists of at least five centers of excellence in autism research. The participating NIH Institutes are as you see here, with NIMH as the lead Institute.

One of the first programs that got started were developmental grants in order to help those institutions which needed some time and resources, to get ready to submit full applications. Those have already been funded, and there were six centers that received those developmental grants, either most of all of which have submitted applications for full centers, which will then be reviewed shortly. I'll show you that in a moment. So after the developmental centers, we did have two rounds of competition for the full centers. The first one has been completed, and two centers have been awarded this fall and are already getting started. Those are at Yale and the University of North Carolina. [Slide.]

Dr. Hirtz: Then for the second and final round of the competition for centers, applications have been received and review is scheduled next month, December 9th and 10th. Then the full complement of centers will be awarded sometime early in 2003. [Slide.]

Dr. Hirtz: So, the total NIH commitment for these centers was $12 million per year, which is a funding pool that will encompass not just the individual centers, but collaborative studies that they do, as well as funding for what will hopefully be a joint center with the CPEA Centers for data coordination. That will include a data coordination within the STAART Network itself, as well as potentially studies or data which may include some or all of the centers in both networks. So this financial commitment doesn't overlap or detract from the CPEA commitment, and as other centers, they will be funded for five years and there will be a competitive renewal process at the end. So, each center was capped in order to make the $12 million total at $1.2 million direct costs with some money left over for

a data coordination center and for collaborative studies. So where we are now is, eagerly awaiting the review in December, and I think we have quite a few really excellent applications, and funding should be available for those centers, hopefully as early as possible in the winter or spring. Does anybody have questions about these?

Mr. Shestack: Last meeting, we discussed the possibility -- there were numerous very good applications, and it sounds like there will be, because people have got a chance to resubmit. People stretching funding, more of these, so I just want to bring that up again, because we understand that it's a substantial commitment. But $1.2 million is not a particularly rich center grant, and to have a couple more of them would make a substantial difference. What you should know here is that one of the things about these center grants is that they were designed to encourage applicants to have clinical care facilities as part of their centers, and simply the application process has made that happen in places where it hasn't happened before. So I'd

hope we'd find ways to encourage that, and funding more of them would certainly do it.

Dr. Insel: Do you have a response to that, or is this is an additional question? Just as a response, I think it's important to remember that the $12 million budget was a floor, not a ceiling. It was a minimum, and so there is certainly the interest in doing more of it, if the budget permits and doesn't offset other needs. So it has to be put within that picture. I don't know if Steve wants to say more to that, or Deborah, but it shouldn't be thought of as an absolute cap.

Mr. Shestack: It's been consistently encouraging on this idea, but as it gets down to the critical period, I want to reiterate that that would be appropriate, given that it doesn't seem like in the last six months there have been any fewer people with autism diagnosed. So it would be appropriate to fund more of them.

Dr. Hirtz: I want to make one additional comment about the centers. One of the very exciting things about these new centers is the plan to develop collaborative studies and take

advantage of the numbers that will be available through having a network, and then possibly even collaborating with other centers, such as those in the CPEAs. So I think that in addition to funding numbers of centers, one of the important things that we will be looking at is our ability to fund large collaborative studies that won't happen any other way.

Ms. Goldman: My question for Deborah was, if you could clarify the focus of the research that these centers will be doing and how that will differ from the centers that Duane -- their research.

Dr. Hirtz: Actually, pretty much. There certainly will be overlap and many of the centers will be doing similar projects. There will be individual scientific projects, but one of the things that was absolutely required of the STAART center application was a clinical research project and the facilities for clinical care and enrolling patients in these from the clinical care sites into these clinical research projects. So that's

kind of the focus and the emphasis, but there certainly is overlap.

Dr. Insel: This is really an important initiative, and, again, part of the same Act that powered this Committee, and will be an important thing for us to follow over the next year or two. I guess the assumption would be that within six months, we will then have at least five of these centers funded, and will be able to look at a portfolio that is quite a bit broader than the one we currently have. Any other comments or questions?

Dr. Zeph: That particular piece in terms of the breadth and scope of the research will be pretty helpful. Is that playing any part in the decision on the choice of the centers; that the research be complementary, so that it's broad enough so that in the Children's Health Act, for example, there were not just clinical pieces that were to be addressed, but if I remember, intervention. So my question is, are we looking to make sure that all of those issues are being addressed?

Dr. Hirtz: Certainly those are fundamentally part of the review criteria for the centers. And as always, when funding centers, they are based on the merit of the applications and programmatic needs.

Mr. Grossman: Maybe taking what John was referring to a little bit further, the advocacy groups that are here -- and I think are very active - I would like some feedback and some assistance, some direction from the agencies in terms of what you would like us to do to encourage more participation and to encourage more funding coming your way, specifically to develop many, many more centers, because I think we need much more than this. This is a great start, and I applaud you for what you've done, but we need many, many more people entering the field, and we need a lot more money going into the field. I'm not sure if this is the forum to do this, but I'd like to get some suggestions on what you need from us to encourage that, and to give us the direction to make that happen.

Dr. Battey: I think you have to take a look at what the rate-limiting step is. It may well be that the rate-limiting step is training new investigators to work in this area. I don't know that, but if you want to make a field go forward, you have to ask what's standing in your way. And, you know, pouring more money into well-funded investigators may not be the answer. The answer may, in fact, be that we need training initiatives to encourage people to take on this important research problem.

Mr. Shestack: The rate-limiting effect, up until recently, has been minimal money for any effort in research. And you can see the difference as some money has come in, and also from the voluntary groups that funded the other studies, the difference being maybe 15 people having finance-able projects, to going to a meeting where there are 300 scientists actively involved in autism. It seems proof that actually a little bit of money applied at the right time, can make a big difference. It may also be just not centers, but may be stronger pilot program funding here that

could make a big difference in bringing more talented investigators into it.

Dr. Penn: I think it's very important that the voluntary organizations -- which you already do -- you speak to the scientists and the physicians as much as we do, almost. Certainly this has contributed to the interest and the acceleration. This is just tremendous. We see this in several of our disorders. It begins to build, one on another. Career development is tricky because it takes time, and we have to get people through the system and keep them in the system. I can assure you that a lot of us are working very hard to do this for a variety of things, including, I have to say, finally, the loan repayment. People will not enter this unless they feel that they have a chance of survival. So there are several things that go into this, but when you provide startup funds for young investigators, when you introduce them to the problems, when you galvanize them outside, it helps us, too.

Dr. Alexander: Dr. Battey made reference to rate-limiting factors. With regard to the

voluntaries, in particular, there is a rate-limiting factor where we need help. That is encouraged by the parents to participate with their children in the research, when asked to. For a long time, this was a major problem. It has been getting better, but more recently it's resurfacing in terms of refusals to participate in research when asked. This has had significant impact on our ability to do a number of clinical studies, running 25-plus refusal rates when contacted to participate. Unfortunately, a major reason that the parents give when asked why, is that they are involved in litigation about causes of autism, and their lawyers are advising them not to participate in any study that might get information that could jeopardize their chances of recovery of damages in a lawsuit. This is becoming a significant impediment to our ability to get the numbers of subjects that we need for research. So any ways that the volunteers can encourage, as they have been doing, parents to participate in research studies, when asked, would certainly help the effort.

Mr. Shestack: I'm surprised, if that's true. There aren't currently very many lawsuits that are actually pending. There are people who are possibly preparing to commence suits, but that would be bad advice given them by their attorneys. We can certainly do something to encourage families. But I do want to bring up something else that we found from our experience encourages families to participate in research, which is the sense that their participation has, in any one study, has potentially a broad effect on the field, which makes me bring up one very practical thing: The CPEAs now have a large number of people. The STAART centers are going to enroll a lot of people. For instance, in our gene bank, we've enrolled now 425 families. And all of those together have the opportunity to be like this gigantic dataset. I'm just addressing the CPEAs and STAARTs becoming the same. It's great to have more people working on it, but just on the level of having the DNA and the phenotypic data in one collection that anybody else can use -- in fact, we could bring in the European groups. It seems

like it would make a lot of sense and not need that much extra work to get everything formatted to make that happen. And it would be a very powerful tool. I know we have already re-consented half of the agreed families to make them go into the NIH bank, and if we all agree to do this, then this really could be something that the NIH, as a whole, decides is something to support, as we try to look for the model complex disorder to do gene/environment interactions. But we need support from all the people in this Committee to do it.
Dr. Insel: I think that's very much in the spirit of what this Committee was intended to do from the beginning, and that is to facilitate coordination in these efforts. It may be worth or while to actually table this discussion, because I think it's one that's going to require a lot more energy and planning, if it's going to have any real impact. But I think the idea of how we can look at data sharing will become really one of the best things that could come out of this discussion.

Before we move on to the next report, I did want to suggest one other thing from the STAART

centers, that it seems to me will be also helpful for the future of the field. Those of us who have been at the IMFAR meetings the last couple of years, it just started two years ago. It's very impressive, how many new people have become involved. And I agree with Jim's comment, training is going to be key and is one of the next steps to get new young, smart people into the field. But another thing that has happened here, which I think is most promising, is that there are a number of senior biologists who are very good neuroanatomists like David Amaral, who are people in other fields are related to neuroscience, who have begun to take an interest in autism. And the STAART Centers have had some role, I think, in helping that to happen. That's been one of the exciting developments. That's one of things that promises to deliver some new discoveries in the field, by bringing in some very powerful senior labs with lots of resources, who have not really been focused on this problem, and can begin to deliver.

Dr. McPherson: Can I also suggest that there is a complex set of service issues related to the centers, and the issue of getting families into research. I think we really do need to talk about that issue, to begin to push and develop more and more centers. It's that issue that young families with young children at this point in time, who are getting that diagnosis or are not getting that diagnosis, and are struggling to understand what the current research is telling them and where the programs are, and getting the children into that research at a decent level of intensity of service, are somewhat overwhelmed with perhaps getting into a research trial which may be quite a ways from their setting. This may not be their first priority. I think we really do need to work with the families and the service providers as we build a service base and we get good programs out there from the research that you have. That's obviously the first priority for those families.

We dealt with it with AIDS, as you know, Duane, in terms of that struggle, and I think that's the same issue here. We've got to build a

service base for those families and help support entrance into research from there.

Dr. Insel: Thanks very much for those comments. Actually, we will revisit this later in the morning. There is a section on a discussion of research participant recruitment at 11:30, so there will be a chance to discuss this at greater length. Let's move on to the third report, which is from Dr. Cordero on the CDC Centers of Autism and Developmental Disabilities Research and Epidemiology. [Slide.]

Dr. Cordero: Good morning. [Slide.]

Dr. Cordero: CDC has -- what I'll do is take a little time describing the centers, but also the other activities that I reported at the last meeting, and see where we are. We have activities on surveillance of autism, on the epi research. We have 33 centers for autism and other developmental disabilities and other cadres, but we also have a collaboration with Denmark that is an important collaboration, which does work autism and vaccines, and also an area that is emerging --

prevention of secondary conditions of autism, which has started in West Virginia. [Slide.]

Dr. Cordero: As a summary, we have 13 states that are conducting, either at the planning phase or actually already collecting data on surveillance of autism. We are funding six programs and one state where we're dealing with secondary conditions. That's West Virginia, as I mentioned. [Slide.]

Dr. Cordero: Our goal in terms of the surveillance activities is to provide a comparable population-based autism prevalence rate in different areas of the country. So, instead of having different areas, we can have a comprehensive view of what is the prevalence of autism, but also have information on what are the characteristics of autism and coexisting disabilities; what are the associated disabilities in these children, as well as what are the epidemiologic characteristics? One question is whether autism is more common in some groups than in others. That's sort of part of the epidemiologic questions. The key question is

whether autism is changing over time. Also, one of the key things that was discussed yesterday in the subcommittee, that I think you'll hear more about later in the day, is how to ensure that we have good identification of people with autism. [Slide.]

Dr. Cordero: In the activities, our network of surveillance -- we call it the Autism and Developmental Disabilities Monitoring Network, and the acronym is ADDM, we are funding a population-based survey and it is starting. In '99, we started with West Virginia. In 2000, we had Arizona, New Jersey, South Carolina, Maryland, and Delaware, actually as one program working together. And there are new programs in Arkansas, Florida, and Utah, plus centers on autism research that are also conducting surveillance. That adds to the 12. [Slide.]

Dr. Cordero: The ADDM Network has a number of activities: One of them is how to collect clinical data, and some of it is from schools sources, but how to expand sources. Actually, what is the best way to address the collection of data? [Slide.]

Dr. Cordero: Here we have the list of the states that in one way or another are planning of conducting surveillance. Georgia and Metropolitan Atlanta was one of the first. And the system that we're using for surveillance was developed in Atlanta by Marshall and Yeargin-Allsopp. I'll talk about the Danish collaboration and NMR participation studies. Let me just sort of review them. [Slide.]

Dr. Cordero: We have six centers. Here is a list of where the centers are: California, Colorado, Johns Hopkins, Pennsylvania, and North Carolina was just recently added, and the CDC in Metropolitan Atlanta also functions as another center. [Slide.]

Dr. Cordero: We are developing a case control study. One of the key objectives of the center is to do epidemiologic studies, looking for epidemiologic clues of causes or risk factors for autism. The groups meet on a regular basis. The last time was in September during our national meeting. We meet again in January. One of the areas is working on developing questionnaires and

the medical abstraction process and data management and also a laboratory segment. We also have collected population-based controls. [Slide.]

Dr. Cordero: This slide talks a little bit about the surveillance activities. They are somewhat different. There are several different approaches to surveillance. There is one in California using their reporting system, and the University of North Carolina at Chapel Hill is using three agencies, developmental evaluation centers, and the Exceptional Children's Division, which is part of the Department of Education in North Carolina. We are also collecting data from non- school sources in some of the states. [Slide.]

Dr. Cordero: We do hope that by the next year, actually that we have the surveillance and the others, but, in essence, we hope to have a protocol completed by the spring of 2003, and, again, the case control study in the fall of 2003. [Slide.]

Dr. Cordero: The collaboration with Denmark is ongoing, and includes many areas, not only autism,

but also thermopulsia [ph.] and others. I was just going to mention that the study was recently published. This is a part of the cooperative agreement. It was just identified. Basically they have the opportunity of identifying all the children with autism in the cohort of about 400,000. [Slide.]

Dr. Cordero: The study, which was published November 7th, basically compared the 440,000 children that were vaccinated with MMR, compared to the 96,000 that were not. In essence, what the study found was that the rate of autism in the group that received the vaccine was essentially the same as that that did not receive the vaccine. That was the case for both autistic disorder and also for the autism spectrum disorders. [Slide.]

Dr. Cordero: This is one piece in terms of data in terms of the question of vaccines and autism. It just addresses the question from the point of view, the parent asked, what is the risk of MMR and vaccines? Overall, basically the answer is that the rate seems to be the same between children who are vaccinated and not. It doesn't

address some of the specific questions being raised about intestinal disorders. Those are being conducted using other studies that are more appropriate. On the follow-up studies, we are looking at a more specific validation of our autism diagnosis, but also following up on the Karen Nielson study on biomarkers, using newborn spots. That's some of the work that we expect to have completed in the near future. [Slide.]

Dr. Cordero: We also, in terms of MMR and autism, we are conducting a study using the data from Metropolitan Atlanta, using the three- to ten-year olds diagnosed or recognized in '96 through the surveillance. This study is almost completed. [Slide.]

Dr. Cordero: The analysis has been completed, and the manuscript has been written and is going through peer review. We expect to have some results in the Spring of 2003. [Slide.]

Dr. Cordero: There are a number of studies that are also being done in terms of thimerosal in vaccines. The screening analysis refers to the study using one of the HMOs or a group of HMOs,

looking at children that received vaccines that included thimerosal. There is a follow-up study planned on those children, as well as another specific thimerosal study, and in the works is also a follow-up of a clinical trial that was conducted in Italy where a cellular pertussis vaccine that does not contain thimerosal, as compared to the traditional PV that does contain thimerosal, and it will be a while before that is completed. [Slide.]

Dr. Cordero: Here are the others: MMR and autism biopsy, basically comparing children that had a biopsy, with autism and without autism, looking at the presence of measles virus particles in those biopsies. We heard a little bit from Duane about the concern about participation, and that is really a concern in terms of the regression study on vaccines participation. It hasn't been as expected, and I think that it's going to take a while to see whether, in fact, the study can be completed. There is another studying going on, trying to get more information and more detailed information about the voluntary reports

on the vaccine adverse event reporting system. [Slide.]

Dr. Cordero: Part of the Children's Health Act also asks CDC to develop an autism information center. We have launched that in September. Here you have the website address. [Slide.]

Dr. Cordero: This is how it looks. It's just a start. We expect it to be expanded, and we actually have links with many, both inside and outside sources on autism. Thank you.

Dr. Insel: Thank you. Comments or questions?

Mr. Grossman: Just logistically, I'd like to get a copy of the presentation.

Dr. Insel: We can do that.

Dr. Cordero: They will be available. I will be happy to have them available for you and for other members of the Committee and others that would like to have them.

Mr. Grossman: Great.

Dr. Nakamura: I had a quick question. What was the preservative in the vaccines in the Danish study?

Dr. Cordero: The MMR doesn't have a preservative. It's a live vaccine, so there's no preservative in it.

Mr. Shestack: Actually, it's not in any of the other vaccine formulations that they use here.

Dr. Insel: Could we just clarify that? Within the Danish cohort, there wasn't the opportunity to do like a DPT thimerosal study? That's wasn't something that could be done or should be done?

Dr. Cordero: The study wasn't specific for MMR, because it's actually the same formulation used in the U.S. The Danish stopped using DPT with thimerosal some years back. I can't remember the exact year, but it was like in the early '90s, I believe.

Mr. Shestack: Thimerosal was removed from most World Health Organization recommendations on vaccines about eight years ago.

Dr. Insel: Other comments? [No response.]

Dr. Insel: If not, I'd like to thank you for these updates. Let's take a break now, because there will be some people leaving. In any case, we'll try to return perhaps a little bit ahead of

schedule, and instead of at 10:15, let's plan to be back at about five after at about 10:05. Thank you. [Recess.]

Dr. Nakamura [Presiding]: Can we begin to take our seats again? We'd like to get going. [Pause.]

Dr. Nakamura: Okay, so next we will have scientific reports from the CPEA Centers. Lisa Freund from the National Institute of Child Health and Human Development will be the introducer.

Dr. Freund: Thank you. [Slide.]

Dr. Freund: I have been involved in our Collaborative Program for Excellence in Autism for about six months now as a scientific coordinator. [Slide.]

Dr. Freund: At our annual meeting last summer, the principal investigators of that group decided that they really wanted to increase the ability of the CPEA to communicate to the community, what they're doing, what the research is accomplishing, and to be more visible so that you know what's going on. One way to do this, it was decided, was to be able to present some of this research at the IACC meetings. So we're planning to have the

presentations, hopefully, at meetings in the future. Today we're very pleased to be able to have two of our principal investigators presenting. Our first presenter today is Dr. Helen Tager-Flusberg. She's from the Boston University School of Medicine. Our second presenter will be Dr. Patricia Rodier from the University of Rochester. Dr. Helen Tager-Flusberg received her Ph.D. in psychology from Harvard. She's currently a Professor of Anatomy and Neurobiology at Boston University School of Medicine. Her background is in developmental psycholinguistics and cognitive science. She's conducted research in autism for the last 25 years, in particular, looking at language development and cognitive development in autism and the related neurodevelopmental disorders. She's an author on over 100 peer-reviewed journal research articles and several books. The overarching theme of Dr. Tager-Flusberg's CPEA program research is to increase our understanding of the interactions between brain function and behavior in terms of language and cognitive behaviors and genes, and how those

interactions can lead to variations in the autism phenotypes and diagnoses of subtypes of autism. Today she'll give us an overview of some of this work, which is really fascinating. Thank you.

Dr. Tager-Flusberg: Thank you, Lisa, thank you for the introduction. I especially want to thank the Committee for inviting us to present today. It's really wonderful to hear about your work and to see, from my point of view as a researcher in the field of autism, how much the work of your Committee is involved in supporting and promoting the funding for research in autism, very broadly defined. I'm here representing the first presenter for the CPEA, which is the longest standing of the current collaborative programs. [Slide.]

Dr. Tager-Flusberg: And what you see here is a map of the United States with the states where the primary site is. In fact, there are many additional states in the United States that are contributing and collaborating with some of these primary sites. And as you will see, Patty and I are representing the East Coast wing today, as opposed to the central or West Coast parts. Now,

we've been asked to present our own work, to discuss both our accomplishments over the past five years, and to talk to you about our plans for the next five years. As we know, we're just at this junction where we've completed the first five years of funding. I'll allude to some of the connections between our work in my program project and some of the other sites. We are not here presenting some of the work on the collaborative projects that the CPEA has been involved with and that both Patty and I have been integrally a part of. So this is really a presentation of our own site-specific science. It's been a extremely exciting opportunity, because one of the things that we realize is how, as we've worked over the last five years, how much our work, which we never thought related to one another, in fact, does dovetail and complement, and where I have the opportunity, I will mention this in my presentation. [Slide.]

Dr. Tager-Flusberg: Okay, so we'll begin with Leo Kanner, and to remind people that we really only have known about this disorder, this spectrum

of disorders, for about 60 years now. And sometimes you might think we haven't -- we know very little, but on the other hand, as someone who has been around for a fair amount of time in this field, we've actually come an enormous way in understanding this disorder. At the same time, I put his picture up here because I find myself, every two or three years, going back to reading Kanner's '43 paper, and I suggest that people do that because he had so many more insights than I ever realized when I first read that paper as a undergraduate and became inspired to study this disorder. [Slide.]

Dr. Tager-Flusberg: Okay, so to talk about autism -- and I don't mean to discuss the diagnostic criteria -- what I really want to talk about here is the fact that we know that there is huge variability in the expression of the three core domains, the three core diagnostic characteristics - social reciprocity, communication, and repetitive behavior -- but, in fact, in addition to this, we also know that there is incredible heterogeneity in the expression of

many features of autism, both in terms of IQ, overall, and particularly the IQ profile -- language affective disorder, atypical behaviors such as aggression or sleeping problems, head size, neuroanatomical organization. And I would say that I think that until about five, six years ago, for many of us in the field of autism, this heterogeneity was a big problem. You know, we were looking for the uniformity. What unifies these children? What's the uniform underlying etiology? What are the specific genes that are going to explain autism in a large group of children, specific environmental influences. In fact, I think what I have learned is that I have to overturn everything that I thought about how we are going to move forward in this field, by, instead of worrying about the uniformity, think about the heterogeneity and not see it as a problem. So, the focus of our research program has been to try and identify meaningful phenotypic subgroups within this heterogeneity, okay? So the idea is that not everyone is going to show exactly the same characteristics. Our strategy has been to

dissect components of specific characteristics such as language, and that's what I will spend the most time presenting today, rather than the earlier approach where we understood there was heterogeneity, but people thought instead of maybe we'll learn something more by dividing the spectrum into, let's say, autism versus PDD/NOS, versus Asperger's Syndrome. Instead, we focus on specific components. Now, our interest, of course, is in understanding the underlying genetics and neurobiology. That's what the CPEA is about, so we're looking for meaningful phenotypes that map onto distinct neurobiological profiles. And then we can ask the question about whether such subgroups provide clues to susceptibility genes for autism spectrum disorders; specifically whether we can link particular genetic loci that have been identified, to particular phenotypic features. [Slide.]

Dr. Tager-Flusberg: So here are some of the examples that we have been pursuing. Obviously, in this brief amount of time, I'm not going to talk about everything we've done for five years, but

I'll be talking mostly about language characteristics, theory of mind, and also face processing deficits. [Slide.]

Dr. Tager-Flusberg: Okay, so let me begin by talking about language. We know that there are universal impairments in communication, in the spoken language, in the pragmatics or the use of spoken language, but also in non-verbal communication and the significant communicative impairments that we see even in non-verbal children. There is, however, among children, enormous heterogeneity in linguistic skills, by which I mean everything but pragmatics, okay, from the non-verbal group of children to what I'll call, with tongue-in-cheek, the super-verbal. By that I mean there are a number of people who have enormous vocabularies, better vocabularies than I do have, who have enormous linguistic skill. So we really run the range from zero to 100 in verbal ability. And just to remind you how important it is to study language, I'm going to be talking about sort of basic research on this, but language is the single most important prognostic indicator

for long-term outcomes in autism, both whether we're talking about verbal or non-verbal, but within even among verbal children, how good your language is, is the best indicator of what your long- term possibilities are for independent living. And so I hope that the work that I'm talking about will ultimately feed its way into thinking about intervention, and I personally am a strong advocate for all people with autism to be receiving language intervention, no matter what their language skills are. Okay, so the work we've been doing is to look at language subtypes, and we've been focusing on verbal children with autism, within which we've identified two broad subtypes. I do want to say that this isn't all there is to subtyping within language. I think Morton Gernsbacher at the University of Wisconsin has been doing some very interesting work on a potential additional subtype of children who have severe apraxia. I'm not including those children in our program project, so I think this is a slice of what we have the potential to view when we try to dissect the language phenotype. Now, in our

group, we've identified children with normal language skills as measured by standardized language tests, so they do very well in vocabulary, syntax, grammar, phonology. They are just fine. But then -- and this is the majority of even our verbal children -- they fall into what I'll call the borderline or impaired language skills on the language tests, okay? So they don't have such great vocabularies, they are impaired on grammar and so forth. And interestingly enough, although it is more likely that the children in the impaired or borderline groups have lower IQs and may have had delayed onset of language, there is not a 1:1 relation. There are children in the normal language group who were delayed in the onset of language, okay? And there are also children within the normal language group who do not have IQ scores within the normal range. So it's not 1:1. [Slide.]

Dr. Tager-Flusberg: This is a graph and it's a busy graph that shows the profiles. And what you see here is that -- this isn't going to work. Oh, here it is. The normal language groups -- these

are all children with autism -- all their scores are in the normal range where 100 is the mean. And for the borderline and impaired groups, they are below. However, a relatively spared group in this particular cohort is articulation, okay? But they were preselected for that, and so that's not to say that other children don't have problems with that. This is among our verbal children.

But, interestingly, we found that our children had great difficulty on a task that we had thought the children would do very well on. And that's called a non-word repetition test. And that was interesting for us because it provided us with the clue that perhaps there are parallels between this language-impaired group of children with autism, to children with other language disorders, in particular, children with a disorder called Specific Language Impairment or SLI. These are children who have delays and difficulties acquiring language that continue throughout their life to have language-based learning problems. But they do not have autism or any other clear neurodevelopmental disorder. This is their

neurodevelopmental disorder, SLI. Now, the clinical markers of SLI have been identified as two crucial deficits at a clinical level: One is deficits on this on-word repetition task that we found our language-impaired children with autism also had difficulty with. You give children strings of syllables like vy-vee-goan [ph.], okay? It's not an English word, and they simply hear this and they're asked to repeat it. It's meaningless. I thought children with autism could do this kind of stuff, and it turns out they can if they have normal language skills; they have difficulty with this if they have impairments as shown on other language tests like grammatical tests. They also have deficits in grammatical morphology. And in English, this is especially clear when we look at their ability in everyday speech or on experimental tasks, to mark tense, to use the past tense ending E-D when they're talking about something that happened yesterday, or to use the third person present tense, like "she goes." Children with SLI tend to omit these morphemes. So we had already found that the children with autism

were impaired on this, so we followed up our original study by looking at, well, are they also impaired on this? And, surprisingly, there wasn't really very much literature on this in the pasts, so we gave a couple of experimental tasks looking at past tense and third person, and in red you see here, these are the children with autism who have language impairment as shown on standardized tests, and the blue are the language-normal group, again, children with autism, but doing much better. So on both our clinical markers, we found that this subgroup of children with autism who have language impairment, show striking parallels to children with SLI. So then we went to say if this is a meaningful subtype with this interesting parallel, does it tell us something about the neurobiological substrate for language in children with autism spectrum disorders? Now, in the normal human brain, the language regions, the Broca, Weinecke's area, inferior frontal cortex, planum temporale back here, or Weinecke's area, these are larger in the left hemisphere. Now, there have been a few MRI studies of people with SLI,

children with SLI, and what they have found is that in SLI, you either find reduced left large or, in fact, reversed asymmetry where they may be larger in the right hemisphere, okay? They did not find differences in the planum temporale. So we asked the question, can we find the same pattern of reversed asymmetry in autism, but, in particular, in those children with language impairment? [Slide.]

Dr. Tager-Flusberg: This is to remind me that we prepare our children for an MRI scan by using a mock scanner. The children are trained for several sessions in the scanner. This is not a real one. They are introduced to it, and they're trained in there to remain motionless, and this allows us to collect a wonderful, high-quality scan without any sedation. [Slide.]

Dr. Tager-Flusberg: And here's a child receiving his prize, and that's how we get them to enjoy the experience. [Slide.]

Dr. Tager-Flusberg: So in our study, we had four groups of age-and-sex-matched boys, about nine and a half; the two different groups of

children with autism; a group of children with SLI, and controls, and we've used methods for segmenting and parcilating [ph.] and being able to measure these brain regions, that were developed by the Center for Morphometric Analysis at the Mass General Hospital. [Slide.]

Dr. Tager-Flusberg: And this is just an illustration of the methods where you first segment the white and gray matter, and then you parcilate [ph.] using central gyrae, using gyrae and other crucial landmarks, parcilate the cortical and subcortical regions. Okay, so what we're looking at in this study, in this particular study that I'm going to mention -- of course, we're doing many other things with these brain scans -- is, we're measuring the size of this region of the planum temporale that's more posterior, and we're measuring the size of the frontal region, the inferior frontal cortex related to language, which includes the pars triangularis and the inferior frontal pars opercularis. Okay, so that's what we were looking for. And what you see here is, we've graphed the

data here in terms of an asymmetry index. And here, anything above this line here, above the zero line, means that the region was larger in the left hemisphere than in the right hemisphere, okay? And anything below the zero means that it was lower -- it was larger in the right hemisphere than in the left. And what you can see is that these are our normal controls and our children with autism, but with normal language; and you can see that they're showing the predicted left hemisphere asymmetry in the frontal -- this is the frontal region. However, both our SLI children and the children with autism with language impairment are both showing this right asymmetry. Interestingly -- and I think this is the first study to demonstrate, also for SLI -- is that they showed an exaggerated left hemisphere asymmetry in the posterior regions of the brain. So then we can ask, is there functional significance to these differences in what are essentially structural asymmetries? And we've been used functional MRI methods to investigate the neurosubstrate for language processing in adults with autism, so

these are now not the same participants as in the studies I have been talking about so far. And in this study, we have compared 24 controls to 16 adult men, and they are matched on age, and they are all right-handed, I think, in this particular study. And what we do is, they are lying in the scanner and they see words appearing on a screen. And we've made sure that we've screened that they can read all these words, and these are all high-functioning adults with autism, and they are providing then their own consent for participation in the studies. And they see words presented, either in upper case or lower case. And there are three groups of words. I'll come back to this later in my presentation. For the first part, it really doesn't matter. They were concrete words like "animal," "table; mind words, words like "think," and "known;" and abstract words, which -- mind words are also abstract, but the abstract words were non-mental like "justice." And the task: They have two different tasks that were blocked. They either had to say other letters in the word presented in upper/lower case or a

semantic judgment where they have to do some real language processing, not just visual processing. They had to judge the word, whether it was a positive or negative word. And here what I'm showing you are the activation patterns for the semantic tasks where we remove whatever activation we see, whatever brain activity occurs, to just looking at words in general and making the upper and lower case judgment. And up here we see the activation pattern in the control participants. And what you see is that there is very robust activation in the left inferior frontal cortex. And this is really a replication. This is a task that has been used in a number of FMRI studies, quite a lot. So this is just essentially a replication in our controls. And we do have some weak right frontal cortical activity, but it's much weaker than in the left, as expected. And down here we have the activation from the participants with autism. In fact, there is some activity in the left inferior -- left prefrontal cortex, but it's very weak, and I think it's not even observable to you back there. I can see it

because I know it's there. But what you also see is that it's not left-lateralized; it's most certainly bilateral, if anything. So we can see then that there seems to be these differences then, these structural brain differences leading also to differences in activation patterns. Okay, now, this reminds me then to talk about what are the potential genetic implications? [Slide.]

Dr. Tager-Flusberg: This is a summary slide. All these red dots are loci that have been identified across multiple studies that have done genome scans. And as you can see here, on Chromosome 7, we've got lots of studies. This is the number of studies that have identified regions of interest. And another chromosome of interest to us here is Chromosome 13 because that's also been linked to SLI. Both 7 and 13 have been linked to SLI.

So, we ourselves do not have a genetic study in our program project, but Susan Folsten, my co-PI on this -- and we collaborate across, and of course, with the wider autism community. Linkage analyses have identified susceptibility genes on 7

and Q for autism and also for SLI. And there have now been two studies reported, one by the CLSA and one by the Agree Group, showing that if you now take your large sample of families with a child or more than one child with autism, and you take out those families that have normal language, identified in some way or other, have better language, and you're now left looking for linkage signals just with the more language-impaired group, in fact both these studies have reported and increased signal, but two on 7Q, and the CLSA also found an increased signal on 13. So we see how there is this real potential then for having identified these different subtypes for informing both our neurobiological studies, as well as genetic studies in the field of autism. Okay, future directions: So where are we going in our program project with this? Well, we're continuing to compare autism and SLI, dividing our autistic children into these different subtypes in tasks that tap language processing. But SLI is not the same autism and there are language impairments that we know or we predict are really distinctive

between these groups, and so we're going to also be looking at other kinds of language processing tasks. And then, finally, we're going to, with the same children, now move our FMRI, our functional imaging studies, down to children, and compare activation on language tasks in children with autism, SLI, and controls. We are also doing structural imaging studies and we're very excited about introducing diffusion tensor imaging, which is going to allow us, in particular, to look at the connectivity between the different language regions, especially that green and orange region that I pointed out earlier. Okay, another important piece of our program project has been the focus on theory of mind deficits. And for those who don't know the sort of classic way of diagnosing a theory of mind problem in a person is something called a false belief task. You show someone this Band Aid box, all closed up, and say, what do you think is inside? Of course, you'll say Band Aids. Then you open it and show that there's a car inside. Now, I close the box and I say to you, well, when I show this to Dr. Insel when he

comes back in, I show him this box all closed up like this, what and will Dr. Insel think is inside the box? Or what will he say is inside the box? And if you pass this task, you'll say, well Dr. Insel will say Band Aids. And failing this task says that Dr. Insel will say there's a car inside there. Now, it is this kind of task that has been used to really propel this theory of mind hypothesis of autism. So, the idea, which now has been around for a long time, is that autism involves fundamental deficits in understanding other minds; that people do have mental states that motivate their actions: Belief, intention, desire, emotion. And we know that children with autism do fail these tasks; that's not new. But we've also known from the beginning, from Simon Behrenkorn's original study, that some children always pass this task. Now, one way of looking at that piece of evidence is to say, oh, so theory of mind is not the problem in autism. Our approach has been somewhat different. We're interested in what explains this heterogeneity. Why do some children pass? Why do some children fail? And,

more importantly, I think, what has emerged from our work is the question of how do they pass the task? So we've been doing the longitudinal study of children age four to 14, and I think one of the problems with this has been an overemphasis on the false belief task that I showed you. And, instead, what we've done is to develop what I think is probably the largest battery of theory-of-mind tasks. We have ten different theory-of-mind tasks and they span theory-of-mind debilities that go from 18 months, understanding very simple kinds of pretense, to 12 years of age, so it's a much broader developmental perspective on theory of mind. And in addition to giving these children these theory-of-mind tasks, we gave them language executive functions and IQ measures. And we've tested these children over three years with the same tasks, although they didn't see the Band Aid box every year. That got changed. So what are our main findings? And this is actually the first report in the literature; we did find that the majority of our children showed developmental gains. The child who failed Task A in Year One,

didn't continue to fail the second year. We showed that children got better over time, so it's not an all-or-none phenomenon. They're impaired in this domain; it's not absent. And I say this here because I think people often talk about the theory-of-mind hypothesis as if people with autism do not have a theory of mind. And it's not that; it's more heterogeneous, even within that. Now, the single predictor of developmental change and of who would pass specifically, the false belief tasks, was, in fact, language and specific knowledge of a particular grammatical construction, which I'm not going to go into here. But we were interested, okay, so language seems to be the key. What's happening in functional imaging studies? This means -- this is sort of suggesting that people with autism, when they're passing a theory-of-mind task or when they're thinking about mental states, may be doing this via language, and not via the neural systems that have evolved specifically to handle theory of mind, and more broadly, really, social information processing, the social brain, as Leslie Carruthers calls it.

So if you go back to my FMRI study I mentioned before, remember that we had mind words and abstract words. In our controls, what we found was that the mind words activated two crucial regions that have been associated with the social brain -- and I'm sorry it doesn't show up here -- the orbital frontal cortex, and the superior temporal gyrus. And we see pretty robust -- except my green arrow is obscuring it here -- activation in those regions. In autism, we found very weak bilateral activation in a number of spots, but nothing in orbital, frontal, or in the superior temporal gyrus regions, suggesting that when they are processing theory of mind, they're not doing this quite the way that the controls are doing it. So this has led us to think about theory of mind and how do people with autism get there. Now, this is really sort of a cartoon developmental model for what's going on in the typically- developing child. And what's so crucial is the attention to social stimuli, especially faces, voices, also body gestures and movement. This leads to their ability to process faces, facial expressions of

emotion and other mental states, and also vocal expressions of this. It also feeds into language, but language is tied to other independent cognitive mechanisms. In autism we know there are fundamental impairments. I'll talk a little bit about their work on processing eyes in a minute, to end my presentation. But in autism, this whole piece is what's really -- this is what's a core impairment. But some people can get there, but they do so via language. Okay, well, let me talk about our work on face processing. This is data from a study done by colleague Robert Joseph. You show a person a face. You've all had a good look at it. Now you see these two faces. Can you tell me which was the face you just saw? Okay, well, I think it's this one. I practiced that this morning. I'm not very good at this task.

[Laughter.]

Dr. Tager-Flusberg: Okay, and what we did from the recognition trials, is, we either changed the eyes, the nose or the mouth. It's a much more complicated design, but you can sort of see what the idea here is. And these were relatively high

functioning children about nine to 12 years. And here are the data from the study. Don't worry about all the little paragraphs, but what you can see here is that when they had to recognize the face based on the mouth, it turns out they're not so bad at this. They're getting 70 percent correct, and this is a pretty hard task. But when they had to recognize it on the basis of the eyes, they're doing pretty poorly. There is a significant difference here. And what you find is here, where I'm comparing our controls just on the eyes trials, you can see that the children with autism are significantly impaired on recognizing faces based on the eyes. They are not impaired when we compare them on the mouth trials, okay? So we see then that there's real aberrant processing of eyes. And this fits very nicely with some of the work being done by the Yale CPEA, as well. So, what are the future directions for this particular line of work? Because, if you remember my developmental cartoon of theory of mind, being able to focus on the eye region of the face is crucial for developing social abilities, including

theory of mind. We're going to stop by looking at, well, maybe if you cue children, we'll find that they perform differently and that they are able to do better, if we're training them to cue them on the eye region of the face. Another thing we're interested in is eye gaze. This is something that's been around in the autism literature for many, many years, about 30 years or so. And we kind of go back and forth on studies of eye gaze, but we're now planning to go back, along with some of the other CPEAs, to look at this in a little bit more detail, and, in particular, ask, can children with autism use, whether a person is looking at you, looking away from you, can they make that distinction? Do they understand eye gaze as a cue. And what we're doing in our studies now is, we're complementing our cognitive behavioral methods with eye tracking and electrodermal response, to see exactly where do children with autism -- where are they focusing on the face, okay? And how are they responding physiologically? Do they find it more arousing to look at a face than non-social stimuli? Do they find it less

arousing? And we're interested, in particular, in the individual differences on this and how that will relate to their social adaptation. We're also planning to do some functional imaging studies. These are scans that are taken from our ongoing adult studies. These are not fully analyzed. What you see here is, we've compared -- we just show it's a passive viewing task, eye emotions and mouth emotions such as disgust, where you sort of look at the mouth to distinguish a disgust emotion, whereas fear and sadness are mostly expressed in the eyes. And what you see here is that in the adult controls, we get quite robust right -- because this a reversed slide -- amygdala activation, and also a very interesting cerebellar activation to these eye emotions. And we're not getting activation in these regions in the adults with autism. This is very preliminary, and that's why I haven't expanded on it. But we're going to take this further, and we're particularly interested then in taking our behavioral paradigms and also looking at this in our functional studies. So, to summarize, our approach has been

to dissect the symptoms of the phenotype of autism into subtypes, particularly in the domains of language and social communication. That's the focus of our program project. We use this to inform our structural and functional imaging studies, and we're interested in the potential implications for research on genetic and other etiologies. I must end by talking about all the amazing people who have contributed and who have really been a privilege for me to have the opportunity to work with. Some of them are new to the field of autism and are moving on to stay in the field of autism. Some are more established researchers in the field. Without this group of people, I wouldn't be presenting this work today, and then, of course, without the support of the CPEA, and, in particular, the NIDCD, which is funding our program project, and my program officer at NIDCD, Dr. Judith Cooper, who has been an incredible source of support. Thank you.

[Applause.]

Dr. Nakamura: We have a few minutes for questions and comments.

Dr. Cordero: Very interesting work. On the theory of mind, do you have some of the questions that, instead of there being one step, say they're a two-step process? If so, are there differences when you look at children and individuals with autism?

Dr. Tager-Flusberg: Yes, because it's a sequenced battery. One way we do that is, we have two different kinds of false belief tasks. One is, if you'd like a single step is, what will so and so think about this? This is a more advanced task. Quite a few children can pass that task. It's what will so and so think about what this other person thinks about X -- I'm very bad at coming up with examples off the top. So, what will mom think Joey bought for her birthday? That's one of the stories, for example. Again, you find that the majority of children with autism, even the high functioning ones, are failing that second one, the two-step one, but some do pass. It's not a complete, all-or-none phenomenon.

Dr. Carbone: I think it's very interesting. This is exactly what I was thinking when you were

talking about how language provides a work-around for a basic defect. Some interesting on basic defects in social communication came from nonverbal situations in pre-verbal kids. Or if you remember these recent animal studies, you take the wolf versus the domesticated dog, where the domesticated dog actually shares a theory of the mind, because it understands that a tap of the box means there's food inside. And the wolf would be the autistic equivalent, because they don't catch that clue. I think that will provide some very interesting background.

Dr. Tager-Flusberg: What's most interesting about those studies with animals that can understand some of those kinds of signals, is that there seem to be species differences in their ability to use eye gaze. This is work done by my colleague, Mike Tomasello in Germany. You find those same species differences. Dogs are actually very good at cluing into eye gaze as a cue.

Dr. Carbone: Domesticated dogs, whereas the non-domesticated animals were not. And it wasn't intelligence-based, because chimps, which are

obviously smarter than dogs, did not have the hardware.

Dr. Tager-Flusberg: That's why we think this work -- these are in separate lines, but I actually want to emphasize the importance of being able to do what seems like two streams of work, face processing and language, in separate projects. However, having this wrapped into what, in our case, is a program project, but in the STAART Centers Program will be centers' projects, allows us to draw unique connections across different projects people are doing, because we are able, within this framework, to collect on the same cohort, such rich data. Really, we're finding things out that we did not go in there looking for to start with, but they're there, if only because we have that kind of data available. This is something that's happening across all the CPEA sites, because we've now got five years' worth of data. I'm glad you've seen those connections. That really is something that's sort of the hidden benefit, being able to draw across that way.

Dr. Kellan: I can think of one very pedestrian application of your research. I think we know how difficult it is to toilet-train individuals with autism. The implication of not being able to process an expression of disgust or perhaps the language that might go along with that, which typically children use as they self-regulate, eventually, may be a piece that's missing, the module dealing with disgust.

Dr. Tager-Flusberg: We don't really know. We haven't looked at that in our children. We actually found in our adults -- I just showed you a clip of the SMI study. When we looked at their activation pattern to the so-called mouth emotions that included disgust and happy, in fact, the adults with autism actually showed the same activation patterns as the control subjects did. But, of course, these are high- functioning adults who are, at this point, toilet trained. I don't know. I think it's a very interesting question, whether disgust -- I mean, I understand from my colleagues in the field of emotions that disgust is an emotion that has probably a distinct

processing pathway. We don't know what it's like in autism. I don't know, but maybe other people here do know of work on this specific point.

Dr. McPherson: This is somewhat along the same line of what I'm going to continue to ask over the next few days: Can you take that research for practice in terms of what you know now, if you were talking to speech and language people, and what is happening to make that happen?

Dr. Tager-Flusberg: I spend a great deal of my time doing rounds, speaking to parent groups, especially in the state of Massachusetts, and particularly professional groups, especially speech and language people in the school systems, and also through their organizations. One thing that I think is really crucial right now if you have a child with autism whose verbal, they'll focus on assessing pragmatics and putting them in pragmatic skills programs, which is wonderful. But what they are not doing is assessing their language skills from the point of view of you compare the spectrum. These verbal language-impaired children, they're verbal. They've got

some language, but the piece of their language impairment is being very much ignored; it's not necessarily being assessed because the assumption is, oh, this is a child with an autism spectrum disorder. I need to focus on pragmatics. They're ignoring that and it's really the majority of verbal children with this language impairment who will benefit from social skills training and from pragmatics groups. But that intervention will not improve their language skills, and they need to have access to the same kind of services that children with SLI may or may not be receiving. I have to say services altogether for this kind of language impairment are pretty poor out there. But, yes, I think it's very important. It suggests that a language assessment must be much broader than what many of these verbal children are currently receiving. But again, I do want to remind you that I'm looking at one end; I'm looking at the verbal children. And I think what we really need also is an emphasis on the nonverbal and trying to understand what those subtypes look like. What's the neurobiological

substrate there? Is it the same as in my language-impaired children? Is it different? That's where I think we also will be going, but there's only so much that one program project can do.

Dr. Nakamura: We're going to have to press on to make sure we have time for the next speaker.

Dr. Freund: Thank you so much. We are going to now hear from Dr. Patricia Rodier. She received her Doctorate Degree in Psychology from the University of Virginia, with subsequent post-doctoral work in the area of embryology. She's currently Professor of Obstetrics and Gynecology at the University of Rochester. Her background is in understanding the development of the central nervous system and the impact of environmental insults such as toxins on the development of the central nervous system. She's been studying autism for many years and the theme of her autism research is based on the premise that the animal models can facilitate our quest for really finding causes of autism and the best treatment for autism spectrum disorders. We need animal models because the function is not only biologically similar to

humans with autism, such as genotype analogies, but also that function behaviorally similarly. And then that we can unpack the variables involved in our environmental exposure, gene interactions that can lead to behavioral deficits associated with autism. So Dr. Rodier if you could please join us?

Dr. Rodier: Thanks very much for the invitation to talk to this group today. Many of the things I'll be telling you about from our CPEA will sound very different from what Helen presented, because ours is the most biological orientation of the CPEAs, and yet, as she pointed out, we also have many things in common. In fact, her group has been working on dysmorphic facial features, as we have. We've been working on new ways to look at narrative discourse, as she has. So, the connections are much greater than they may at first appear. Okay, because there are so many people interested in suspected environmental factors in autism, people often forget that there are known environmental risk factors in autism. And these are the one that have been confirmed in epidemiological studies. The first one discovered

was rubella, discovered in the '70s. This is only with exposure in the earliest part of the first trimester. Then thalidomide, discovered in -- first reported in '84 -- excuse me, '94. Thalidomide, as you know, causes limb defects, but the rate of autism is quite high among people exposed to thalidomide, if they were exposed during the fourth week after conception. Valproic acid is an anti-seizure medication, now used also for headaches and bipolar disorder, unfortunately. And valproic acid, according to the facial features, we think, probably also requires exposure in about the fourth week post-conception. Ethanol has been reported in three different studies, but it's only ethanol at the level and with the timing that produced fetal alcohol syndrome. So that's very early, probably the third or fourth week post-conception. Misoprostol is the most recently reported, and misoprostol was discovered by Marilyn Miller, working for our CPEA. This is an abortifacient used in South America, and in this case, the exposure occurs in the sixth week of pregnancy.

Now, just looking at this list of five known factors in autism, tells embryologists and teratologists a lot about at least some cases of this disorder, because what they have in common is that they have different mechanisms, but they have very similar timing; that is, it suggests that it's something around the time of neural tube closure that can cause injuries that can lead to autism in some, if not all cases. And for those of you familiar with the developing nervous system, you know that there is very little nervous tissue present at the time of neural tube closure, and so it helps focus our attention on the earliest-forming parts of the brain as possibly being of interest in autism. Now, here is the program that we set up to take advantage of this embryological information. We have Project 1, animal models of autism and mechanisms of injury that's led by Lorraine Gudas and me and Christopher Stodgell. And this is one where we want to develop animal models. We have genetic models and environmental exposure models. Project 2 looks at both humans with autism and at animals from the models

developed in this project, and the leaders of that are Susan Bryson, Dalhousie University; Mark Stanton in Delaware, and Jane Herbert in Delaware. Genotype/phenotype in autism and behaviorally-related disorders is led by Susan Hyman at Rochester, and involves our geneticist, Denise Figlewicz, Marilyn Miller, the person who did the original thalidomide study, Susan Bryson, and a number of others. And this is a cluster study in which we're not only trying to divide the autism spectrum into possible subgroups, but we're actually looking over a number of behaviorally-related disorders, including specific language problems and Moebius Syndrome, which I'll tell you more about later, to see if the diagnostic boundaries or etiologic boundaries are properly placed or improperly placed. Finally, we've been funded for a new project in the next cycle, and this one is to look at gene/environment interactions in exposed populations, so we're going to be taking people, groups of people who have been exposed to, say, thalidomide, in utero, and we're going to be comparing the genotypes of

those who were later diagnosed with the disorder and those who were not. It's likely that some of these environmental factors interact with specific genotypes, as I will show you more in a minute. Okay, I want to give you the flavor of Project 1. The first thing we found in looking at animals exposed to valproic acid during neural tube closure was that we could alter the number of neurons in the cranial nerve motor nuclei and could alter the distance between the facial nucleus and the glossopharyngeal by exposing animals at this period.

So that's one of the things that goes wrong in valproate exposure that might be related to the high rate of autism. So we wanted to look at other parts of that neuroanatomy to see if there were other things related to autism. Okay, here's one. If you look at the inferior olive in humans with autism, there is a deficit in cell number and there are alterations in shape, so we've now done that with valproate-exposed animals, and, in fact, we get the same effect that's been seen in humans, with a big reduction in volume, no change in cell

density, big change in neuron number. So this is a point of parallelism in the anatomy of the valproate model -- this is a rat model -- and the human case. Another thing that's been reported in both MRI studies and in anatomical studies using histology is that there's a difference in people with autism in the size and shape of the cerebellum. And this is somehow changing my spacing, I'm sorry, but, in fact, we get exactly the same effects that have been reported in humans, in these animals; that is, that the vermis is the most affected part, posterior vermis more than anterior vermis. So this is another point of parallelism. Now, you notice I'm talking about cerebellum and inferior olive. Well, one reason we're so interested in that is that in Project 2, where we're looking at simple behaviors, we had reason to think that the conditioned eye blink might be impaired or altered in autism from an earlier report by Sears, Benn, and Steinmetz. And so we have been working very hard to set up human studies of eye blink conditioning and parallel animal studies. The reason that this task is so

valuable and so interesting to us is that every step of the pathways involved in it is known from animal lesion studies. So, does everybody know what I'm talking about? This is pavlovian conditioning like ringing a bell and the dog salivates? But, in fact, this is going to be a tone and a puff of air to the surface of the eye that causes a blink. And after many, many pairings of the tone coming in the ear and the puff coming to the eye, the person will start to blink before the puff. So you can tell a conditioned eye blink from an unconditioned one because it occurs earlier and it has a larger amplitude, okay? And I'm going to show you a little movie of how we do this. Let's see, you're going to help me with the movie, but I don't want to start just yet. I want to explain a little bit. What you're going to see is a young man being conditioned to blink to a tone instead of waiting for the puff to hit his eye. And all he has to do -- he's not aware of anything that's going on. All he's doing is watching Shrek, which you may hear in the background, and wearing our funny hat. And he'll

be subjected to trial after trial. Now we're going to show the movie. [Video presentation made.]

Dr. Rodier: The blinks you're going to see are unconditioned. They're going to be in response to a puff. But I think the next one, there's only a tone and no air puff. No, there was a puff, okay. So that was an unconditioned. The next one is going to be just a tone. There was the tone and he blinked. Okay, so that was a conditioned response. So here's what happens when you look at people with autism on this task. To everyone's amazement, they acquire the conditioned response more rapidly, and they reach a higher level, and in a second session a week later, they maintain that higher level. Now, interestingly, if you remember my picture of the cerebellar cortex, we know for certain that the timing and the amplitude of that blink, the conditioned blink, are dependent on the Purkinje cell-granule cell in the cerebellar cortex. The association itself is dependent on the nucleus interpositus, so we know exactly where these things are being controlled, and, of course, the fact that they condition very well and they

have too rapid timing, implicates cerebellar cortex, just as the histological studies have implicated cerebellar cortex. We've also just finished analyzing the data of a third session where we changed the interstimulus interval time, and we now know that people with autism extinguish much more quickly than people with no diagnosis. So, there are some very unusual things in humans with autism and eye-blink conditioning. But here's the best part; all of that occurs in the animal model as well, as animals exposed to valproate during neural tube closure not only condition more rapidly and reach a higher level than saline controls. They also have an oddity of timing; they blink too fast, and thy have a very high amplitude of blinking. Now, this task can be altered in many ways to test other parts of the brain, and those are among the things we'll be doing in the next few years. I should also mention that the Colorado CPEA has also started using this task, and Mark Stanton from our group went out to Colorado and helped them set up the equipment and learn how to code the sessions. So that's typical of the

collaborations between the CPEAs. I'm going to show you one other simple task, and this is one developed by Susan Bryson at Dalhousie University in Canada. This is an orientation task, and here's what it is: The child is going to sit in front of three screens. The first screen comes on, then it goes up. The child's eyes go to the flashing lights. The second screen comes on, and the child's eyes switch to those flashing lights. Okay, and children will do this when they are just a month or so old. When they get to be in the third month, they develop a new ability, and that is, if you leave the first screen on and then put on the second, they can disengage from the first and go to the second. But children with autism never develop this ability, and this task, so far, is 100-percent diagnostic of autism spectrum disorders. So now I'm going to show you first, a child with Down's syndrome and an IQ of 20 doing this orientation task, and then a child with autism who has an IQ of 100 and is five.

[Videotape presentation made.]

Dr. Rodier: This is the girl with Down's syndrome, but I'm going to back it up, okay?

[Pause.]

Dr. Rodier: The little girl with Down's syndrome, you're going to be watching her eyes. If you can see two lights, then it's a disengaged task; if you can only see one, it's a shift task. But you'll see her eyes move very smoothly. That was a shift. That's a disengage, because there are two lights in her pupils. That's a disengage. She's has excellent pacifier skills, too. Now, when the little boy comes up, you're going to watch him get stuck in the middle, and you'll see that he's in some discomfort. Babies, as they are developing this ability, also show discomfort. There's the second light, and he's stuck. Now he looks away, but, see, there's some unpleasant about this, but we don't know what it is, but the babies will whimper and they show shallow, rapid breathing. Okay, so that's the end of that one. Now, Dr. Stanton and Dr. Bryson and I have worried over this task for some time, almost five years, and we have decided that it's not a good task for

rodents, unfortunately, because visual stimuli are just not as compelling for rodents. It would be a great primate task, and we might try to get some funding for that. However, what Susan Bryson is using it for now, is, she's using it for early detection in children at risk. Because it's been 100-percent diagnostic, so far in over hundreds of cases, she's looking at children who are siblings of children with autism and at five months, about 30 percent of those children are positive on this task. So if that holds up, we may have a way of detecting the ASDs much earlier than we've been able to before. Now, I'm going to talk quickly about how looking at the brain stem got us into the business of looking at early developmental genes. And this is a paper that was published two years ago, and I will just show you quickly that we discovered a new allele of Hox A-1, the G-allele, and you can see that people with the GG combination are pretty unusual, significantly so, suggesting that there might be some impairment of viability. That's actually been replicated in at least four studies, and then not replicated in a

couple of others, including in the CPEA samples, so samples are different. But the most interesting thing we found was that this is what's called transmission into the disease; that is, in affected children, you see a high rate of that G-allele, but in unaffected children in the same families, you see Mendelian expectation; that is, there's an even split of whether they get the G- or the A-allele when they have a chance to get either one. But the most interesting thing is that this effect is almost entirely due to when children get the G-allele from their mother. It's not so prominent when they get it from their father. And the reason that's very interesting to those of us who are into brain development, is that many developmental disabilities are already know to take this pattern. We know Prater-Willi and Engelmann's are dependent on the source of the abnormal allele, and so this isn't -- it's a surprising finding, but it's not really an unexpected finding. And just recently this summer, we presented data to show that you get the same pattern with Hox-D-1, which is one of the known

risk factors for Duane's Syndrome, one of the features that is seen in autism, and especially in autism after thalidomide exposure. Now, Duane Alexander pointed out earlier that none of this was replicated in the CPEA sample, but it was replicated in the Coryell sample, which is a larger sample. So, people will find it's -- all these candidate genes are going to be found significant here, not significant there, until we figure out good ways to stratify. So, like Dr. Tager-Flusberg, we're working hard to do that. Many of the effects on craniofacial features in autism look to us like pattern formation interruption, and so I want to show you. Hox A-1 is one of the major genes that starts pattern formation in the hind brain, and it's only on for a few days in rat gestation, probably for about a week in the human, and it's never on again. That's all it does; it's a transcription factor; it comes on very briefly; it goes off. And now I'm going to show you what happens to Hox A-1 expression if you expose an animal to valproic acid. If you expose them to saline, you get nothing. These are hours

post-treatment, right? So this is different from the graph I just showed you before. And now we're going to look at retinoic acid, one of the most potent teratogens ever know and you can see that after six hours, you get a tremendous increase in Hox A-1 expression. This is known to be the cause of retinoic acid's teratogenicity. There's valproic acid. At teratogenic doses, it's a much better drive for Hox A-1, even than retinoids, so we suspect that this is one of the reasons that valproic acid is so teratogenic to the nervous system and related to autism also. I mentioned Moebius Syndrome earlier. Moebius Syndrome is defined by dysplasia of the 6th and 7th cranial nerves. Those are the ones that move the eye to the side, and that innervate the muscles of facial expression and some of the swallowing and throat muscles. It's both genetic and environmental in etiology, and it occurs in about one in 20,000 births. We knew when we started our program that there was good evidence from Sweden that there was going to be a high rate of autism in people with Moebius Syndrome, and that study was published

last summer. This is the Swedish study. The ones are positive for autism, six; negative, 17, so about 26 percent come up with the diagnosis of autism. Our study is now up to 40 cases, but at the time I made this slide, we didn't have that many, and we got about a 30-percent rate of autism in Moebius, so there's something about injuries to these cranial nerves, probably at their start in the brain stem, that has something to do with autism. And now I'm going to show you Marilyn Miller's study that I love, which is -- I told you Moebius Syndrome could either be genetic, and it's known to be heterogeneous, genetically, just like autism, or it could be due to environmental exposures. And we can reproduce that in animals. Okay, Marilyn Miller was aware that there had been really an epidemic of Moebius Syndrome in Brazil. And the reason was an abortifacient called misoprestal [ph.], which is used by poor women to attempt abortions. Now, we know that misoprestal is a prostaglandin. Its mechanism has absolutely nothing to do with the kinds of mechanism you see with things that affect pattern formation, that

sort of thing. And they took it in the sixth week, so our question was -- that's a little later than the other exposures need to occur. Our question was, was people who have Moebius Syndrome after misoprestal have a high rate of autism, or will they be different? If they do have a high rate of autism, it certainly suggests that it's the location of the injury that's important. If they don't, it would suggest that it may be some common mechanism or common timing in the other thing that are environmental factors. Does anybody want to guess? I know you don't know, because it's only been published in Portuguese. [Laughter.]

Dr. Rodier: But it's coming out soon in English. Okay, the idiopathic cases and misoprestal cases have exactly the same rate of autism, so this suggests that the location involved in the location of the facial nucleus and the abducens nucleus is very important, at least in some cases of autism. Now, this is our new project, and I'm sorry that something in these program slides things around, but what we're going to do here is, we're going to Sweden, we're going

to Brazil, we're going to Boston, and we're going to examine about 100 exposed cases in each location. We can probably get more, actually, in Brazil, and we might be able to get some more in Holland. I've had some offers for the thalidomide. And what we're going to do is take every candidate gene that's been proposed, and look all those people, genotype them for all those candidate genes, and see which ones may interact with these exposures. In every case where we've seen an exposure that increases the risk, it never increases it to more than like 30 percent, so far. So we suspect that this is a gene- environment interaction, and we'll be able to test that directly and test more candidate genes as they are proposed. So thank you very much for your attention. [Applause.]

Dr. Nakamura: We have time for a few questions.

Dr. Cordero: Great work. One of the interesting points that you bring out is that when it comes from the maternal side, you pointed out that it could be something like you see in

Engelmann's and Prater-Willi. But also the other part is that you have, for example, certain kinds of susceptibility and then combined with an exposure of something like expoxyhydrolase and some of the anticonvulsants; how do you sort out those two possibilities, that it's sort of maternal exposure, maternal genes plus prenatal exposures versus being sort of more like an imprinting?

Dr. Rodier: Well, I think that both of those possibilities, people are showing more interest in. There were a couple of papers in IMFAR about the possibility of imprinting. I think people are starting to think about it. And, of course, this may be one reason the LOD scores are so bad. If it depends on who you've got it from, then you've only got half as good a chance to pick it up, looking at sharing. I think we're starting to sort of get a feeling for how these things might work. I think that in the case of the exposures, the maternal genotype itself could be important. We don't know, you know. And that's the kind of thing that we're after in these studies. In fact, people

have been concerned, for example, that development of the dopamine system in the fetus is known to be somewhat dependent on the mother's dopaminergic status or her genotype. So, you know, there could be many complicating issues. I don't know how many of you know the twins study that came out earlier this year. It's a fascinating study using the Agree sample. What they found was that the rate of twins in the sib pair collection was much too high, about, I think it's three times as many dizygotic twins as were expected, and five or ten times as many monozygotic twins. And what that suggests is that there is some kind of factor that predisposes to autism, per pregnancy, rather than per individual. So it could be a variety of things. It could be environmental exposures of the mother; it could be scarce resources toward the end of pregnancy. We know that there are some genes involved in twinning, so it could be that the twinning genes are related to autism. But I just mentioned this to you to say that the complexity is much greater than we believed five years ago. On the other hand, I'm with Helen. In

fact, having recognized the complexity better, we started to do better. We will do a better job of sorting these things out.

Dr. Gordon: It's excellent work. And this may be a premature question, but is there any evidence of a time factor as to when the abortifacient is taken?

Dr. Rodier: We know exactly. The abortifacient is always taken in Week Six. Every mother was very carefully questioned about. They all took it in Week Six. The facial features of the thalidomide cases with autism absolutely pinpoint the time when they were injured. They may have been exposed constantly, but the time when they were injured was between Day 20 and 24, post-conception, so we know exactly.

Dr. Nakamura: Thank you very much. Next, we're going to have a discussion of -- was there another question? Oh, go ahead.

Dr. Cox: Stuart Cox with the Child and Adolescent Bipolar Foundation. I have a question regarding valproic acid and epidemiology -- actually two questions: Do you have any frequency

data yet on birth rate with children affected with autism, based on valproic acid co-usage?

Dr. Rodier: Actually, Dr. Hansen, who is sitting right here, published the best study or most frequently cited study on developmental delays in children exposed to Depacote in utero. You have to correct me if I'm wrong, but I believe it's 70 percent developmental delays in monotherapy, and 90 percent with additional anticonvulsants. Is that right or about right? I know the 90 percent is right; I'm not sure about the 70 percent. Okay, the study that looked at anticonvulsants in a larger sample of children came out of England a year and a half ago. It's by Moore, Turm, Penney, and others. They had about 46 cases of children exposed, either as a monotherapy or with additional drugs. Of those, six met the criteria for autism. The gene sample was never tested for autism, although their greatest delay was in expressive language, which makes you suspicious, doesn't it? So, that I can -- I have calculated that. It's an odds' ratio of 17, with no specification about the timing. With the study

of thalidomide, if you didn't know the timing, you might think that the odds ratio was only seven or eight, but, in fact, it's something more like 49, if you know the timing. I suspect that valproic is equally damaging. Obviously, some people who are on valproate have to be on valproate, but if there's an option, this is not a good drug for people who are pregnant.

Dr. Hanson: A recent Scottish report showed also a sex reversal in the frequency. I'm quoting other people's data, and, unfortunately, I can't remember the name. But it's interesting that in a follow-up study that was just reported in Baltimore at the American Society of Human Genetics meetings, that in looking at valproate with either mono- or multi-therapy in pregnancy among children who had other effects on fetal development from the anticonvulsant, that there were two interesting things: One was that the frequency of autism was much higher, overall, 20 times greater than in the general population, and, interestingly enough, the sex ratio among the affected children was 50/50, so that the actual

rate for female offspring was 50- fold. That raised questions about an early effect possibly on gene regulatory or gene expression issues, possibly like imprinting.

Dr. Nakamura: Please make part two quick.

Dr. Cox: Okay, the second part of that is, is there -- are there any studies at all on the washout rate for when mothers should stop valproic acid before becoming pregnant?

Dr. Rodier: I would say there are no studies of that. It does clear incredibly rapidly, just an hour or so, so that's not a worry. The only worry is that the timing that we think is critical for it is probably like thalidomide, and so it would be before you know you're pregnant, and so it would be important to stop in planning a pregnancy.

Dr. Cox: Thank you.

Dr. Nakamura: Thank you. Next, Ann Wagner will lead the discussion on recruitment into clinical trials.

Dr. Wagner: We put this on the agenda, actually because in the -- for one reason, we put

it on the agenda was that in our last meeting of the CPEA investigators, there was a discussion about difficulty recruiting into certain trials. And what the investigators asked was, you know, is there a way that we could be better about communicating with the public and with the families about research in general and scientific methods and things, so that we can foster more recruitment or more participation, voluntary participation. So they actually wondered if it would be a topic that we could raise here and try to get some ideas or suggestions about this particular issue. So, I think there are people here who have spent some time thinking about that, and we'll spend a few moments seeing if there are any ideas or suggestions about that. Anybody?

Dr. Gordon: I'm both a parent and a recruiter of research subjects, and we have found difficulties. I wondered, since we have researchers around the table, maybe I'll pose the question, what problems have they found? We found barriers where people just don't want to take the extra time and don't realize that it might be

beneficial, even potentially to their own children, although that obviously can't be promised. I just wonder if there's specific problems that have been found in terms of specific studies or a general ennui in terms of recruitment.

Dr. Wagner: Anybody who wants to take that one up? Okay, Helen.

Dr. Tager-Flusberg: Well, in general, for our CEPEA, we've not have difficulties recruiting. You know, I analyzed that question. I thought I would, and then we were very much inundated with participants. I think there are two reasons why we've actually had a lot of success, one of which I think couldn't necessarily be translated, but the other one, which can be. The first one is, we're focusing on language. That's in our title, and all families, no matter where their child is on the spectrum, they're very interested in that. But I think a second piece is what's helped us maintain them within our language cohort. It didn't make them interested in some of the other collective studies that we've been trying to

recruit for. That is that we spend an enormous amount of time with our families. It's not such a research program, but we're providing a great deal of support to them. We provide them with very detailed written reports, unlike school reports that they get. We make great effort in describing the tests that we've given. It's a research report and we say that's what it is. We describe the tests, and they feel that they are learning. In that sense, they're learning about their particular child. Now, you know, the CPEA projects -- and, I assume, the STAART projects, will have that same advantage. Part of what we're doing is getting into the common measures that Dr. Alexander talked about earlier, so we do provide reports back, and I have specifically recruited to staff our work. I have a family coordinator who is usually somebody that we've had social workers or people in education, so they are able to make the transition for the families between what we're doing and a clinical neuropsychologist who's got training and can make referrals, and also a speech/language therapist.

We find that those are the people that everyone really wants to see. Sometimes they want to see somebody else as a part of a program project, but that's absolutely crucial. At the same time, I will tell you that this is a huge expense that has nothing to do with what the NIH is really funding us directly for. So that's one side of it where I think we have great difficulty, and I don't see how we're going to surmount that. Even though I am now in a medical center that's associated with an urban hospital, Boston City Hospital has everyone there and recruiting someone that's not in my white suburban belt is much, much harder to do. No matter what recruitment efforts we mount -- and we're working on that, and I'm hoping we'll be more successful -- it is extremely hard because of the issues of burden. A middle class family will make every effort and will have the resources to handle the burden, although the numbers of families that are coming in now to our project are bringing along the siblings, for whatever reason, it's very, very hard for them, and, you know, you have to make great

accommodations. But it's not trivial, and I think there does need to be some understanding. I think other researchers need to think about what are they giving back, individually, to families. At the same time, there are enormous costs involved with that.

Mr. Grossman: This whole issue of recruitment was part of a recent NIH-sponsored workshop on psychosocial and behavioral interventions that I guess we had about two months ago.

I just happened to be part of that section, and I'll give you a brief synopsis from the presenters of what we encountered. Recruitment issues, from a parent's perspective included parents being concerned about their children being part of a control placebo group, versus receiving treatment. Also from the parent's perspective was the excessive documentation and/or time commitment, and the experimental research, having their children being used as guinea pigs. From the researchers' perspective, the recruitment issues and problems were identifying or dealing with the heterogeneity of the population; how to handle

concurrent treatments; fostering cross-site treatment and/or pooling of samples, and, obviously, parental involvement, as well as recruiting from under-served populations. Give me a moment here to pull up the slide. I can give you, again presenting from the parental side, what I felt were the necessary means to get parental involvement for the researchers to communicate, communicate, communicate, and also to present that communication in terms of giving us meaningful outcomes. If we have meaningful outcomes, I am sure we'll create a long queue to sign up for the research, and also, as difficult as this may be for researchers, the parents like to be involved, and they want to be involved from the beginning, so try to involve them in the design of the research. One of the other factors which is the hardest thing to produce from the parental side, is getting immediate benefits. Parents obviously want to see immediate benefits, particularly if their child is in the group that is receiving treatment. I thought the best presentation in that section was by Michael Heyman from Ohio State

University. I'll give you his conclusions. He said large studies demand a good recruitment effort, the personal approach, in the flesh or on the phone, get results. Letters do not. Project coordinators, recruiters, principal investigators must be willing to make these initiatives. Shyness is a vice.

Lastly, he said it is good policy to make one person and one arm of the project responsible. This helps to establish accountability.

Dr. Nakamura: Jose and then Rick.

Dr. Cordero: Actually, I think that there are several issues. One is the overall recruitment for general studies, but also there have been issues in terms of recruitment for special studies, like, for example, the regression study. Perhaps the issues there are different. We may need to have a little bit of a discussion of what actually are the issues in the regression study that are different, and what can we do, because it's a study that I think needs to be done.

Dr. Wagner: I think it's very complicated, and it's just the start of what some of the issues

are. We might need to have a subgroup meeting about it and talking about it further, but there's a lineup here.

Dr. Rollens: Rick Rollens, parent and co-founder of the M.I.N.D. Institute at UC Davis. We have a multitude of research programs underway, both clinical and biomedical research at the M.I.N.D. Institute, and, of course, we need lots of subjects. We have had relatively to good success in partnering with parent organizations locally, and, of course, the Autism Society of America, as well. Parents want basically something out of it. If they are going to subject their child to any type of research protocol, they want something in return. And we try, at least at the M.I.N.D. Institute, to work in both the research part, but also work in our clinical side of treatment protocols as well. Again, you almost have to build this sort of state of mind in the community about the need for this, and I think most parents, when they are approached and are approached correctly, are willing to help out the cause. They realize that without this important

research, we're never going to get to the causes of autism and find effective treatments and a cure. It does take, I agree -- I think it was Dr. Rodier who mentioned about setting up a person that needs to work almost full-time on this. It does take time and effort. It's labor-intensive, but you can be successful by partnering with your communities.

Ms. Chessel: Pat Chessel, President of an organization on Long Island, AHA, ASPDD. I'm also on the Board of Education in Roslyn. Michelle Dunn, who is a researcher with the CPEA, did a project -- not a CPEA project, but wanted to do a project apart from CPEA with a board of education, with a school district, and, of course, had a lot of difficulty recruiting a district, but came to Roslyn. And the way we got the parents to cooperate was to give them a lot of information about what she was doing. The project actually is just being published. It's called socialization in our schools. It's incredibly wonderful and it's turned out terrifically. But to give them a lot of information about it, and, more importantly,

assure them that as soon as results were seen, that the control group would be brought on. That was the thing that really got them to stop resisting; that it wouldn't be a year, it wouldn't be two years, but as soon as we saw results, that they would be brought on and that their kids would be part of that. So it worked.

Dr. Wagner: Sybil, then Merle.

Dr. Goldman: I want to reinforce what's been said. My experience with this issue is around work that we've done with children with serious emotional disturbance, not just specifically autism. We worked with the Federation of Families. I just think that there are so many parallels with that work and what we're hearing this morning, which reinforces some of the suggestions made that parents feel very burdened. They need support; they want information; they want to understand what the research is. They want services for their children, and particularly I think, the point that was made about parents who live in urban areas, or who are impoverished. There are special kinds of barriers there.

It does need an intense kind of focus that parallels the research. It's just been reinforced over and over again with the work that we've done with families with children with various kinds of emotional disturbances. So I think there are very good suggestions that have been made.

Dr. Wagner: Thank you. Merle?

Dr. McPherson: Yes to all that's been said. I also would like to kind of challenge the research community to hear what's been said in other kinds of discussions where the discussion was, you couldn't draw the families in, in AIDS, for example. And it came up here today. That is, involve families; involve them from the very first. We have not been able to encourage NIH to any significant degree -- or the academic centers -- to bring families on in terms of articulating what the research needs are in bringing them on. There's a wonderful group of educated families out there that work with us on everything we do, whether it's policy, program, political, whatever. They give us advice. They would very much like to do that with the research community to a greater

degree, and I think you should think about doing that. We haven't really succeeded in doing that. I think the issue of giving something back really is very important in terms of it's got to be a win/win, so it's working with the individual families to find out what they get out of it. The other thing I'd like to mention, though, is that there are some very real insurance issues that relate to getting into research that need to be solved. Number one, when you're talking about the unrepresented families, a lot of them don't have insurance at all. So that issue of trying to get to universal coverage in this country would be incredibly helpful in terms of them being able to move into research. But there is also kind of a Catch-22 in terms of research. Is research -- you're sitting in an HMO that tells you that they will pay for something if it's medically necessary, and if it's evidence-based. So, they tend not to be willing to support what happens to you in research. Now, what NIH funds is the things that their protocol calls for, and therefore you will fund that part, but the other medical

services that those families need don't get done, and they are often related, so that you really need some work between insurance companies and research companies to get some agreement on what are the services that the child and family needs and who's going to pay for those. I think that's an important piece.

Dr. Wagner: Thank you, Merle. We do have to leave this topic, but I want to give Patty a chance.

Dr. Rodier: Lee and others heard me talk about this, but we have been very fortunate with recruitment. We've never had a refusal. The reason is that our clinical service people got together with parents before our CPEA ever started. They pressed the school districts to provide unparalleled services. So, in Rochester, if you're diagnosed with an ASD, you get 27 hours a week of ADA or TEACH or whatever, at public expense. I know this makes other people laugh when they think of the agonies they have gone through, trying to get someone to hours a week at public expense. But because of the effort that was put in by our

clinicians to do this. The parents in our area know that they've already gotten something back, and so they are most willing. I should say that we also have an unusual community. It's mostly scientists, doctors, engineers, Ph.D.s; it is a little rare. However, I should also tell you that the state has become convinced that this program is so cost-effective that they are considering spreading it. It's already being spread to the five surrounding counties, and they're considering making it statewide. So there's a model to look at where you can get some data to show to your school board.

Dr. Wagner: It sounds like communication obviously is the word that keeps coming up, but that there's multiple systems in which one can communicate, and that might be helpful, and maybe we can have some more discussion with some of the voluntary groups about ways to partner with them later. But we're running late, so I'm going to stop with this now. Thanks.

Dr. Nakamura: So we'll take a lunch break and ask everyone to get back here at 1:00. It's been a

great morning, thank you. [Whereupon, at 11:55 a.m., the meeting was recessed for luncheon, to be reconvened this same day at 1:00 p.m.]

AFTERNOON SESSION [1:10 p.m.]

Dr. Insel [Presiding]: Let's get started, if you'll take your seats. Richard Nakamura and I were just joking that we should have actually tried to become identical twins, because he now has to run off to yet another meeting that's going to take him away from here for a bit. He'll try to get back later in the afternoon. We are up to the next session, the 1:00 session, which is an update on one of the Subcommittees. Dr. Hirtz will do the update on the Screening Subcommittee, and Dr. Cordero, are you also going to be involved in that? Okay. [Slide.]

Dr. Hirtz: All right, I'm going to report to you on the Subcommittee meeting that took place yesterday of this Autism Coordinating Committee. This is the Subcommittee that has just formed on early screening. We had a wonderful meeting yesterday. We had not only the Subcommittee members, but participation from a number of

advisors, many of whom stayed and are here today. They were tremendously helpful in discussing issues related to early screening and obstacles to implementing broad programs. [Slide.]

Dr. Hirtz: The members of the Subcommittee are, as you see up here, Dr. Cordero and myself as Co-Chairs, and we have five additional members. [Slide.]

Dr. Hirtz: Basically, the main goal of this Subcommittee is how to implement and actually carry out the implementation of a national broad-based autism screening program. [Slide.]

Dr. Hirtz: I'm going to go over briefly, what we reviewed yesterday, and then tell you about the recommendations and next steps. We started out by talking about what are the published recommendations which had been issued, the practice parameters, by the Academy of Neurology and Child Neurology Society, as well as the American Academy of Pediatrics. These recommendations are quite clear. All children should get developmental screening at all Well-Child visits, and if any child has anything

suspect on these screenings or in the case of some other clear markers of potential problems such as no babbling or pointing by one year, single words by 18 months, or two words by 24 months, or any symptoms of regression at all, that this should trigger a screening for autism, using one of the standard screening instruments such as the CHAT. These instruments are listed on the parameters. The next step is referral for a formal diagnostic evaluation by someone who is expert on the diagnosis of autism. [Slide.]

Dr. Hirtz: We had presentations from some of the investigators from New Jersey who had developed and piloted the First Signs, which is a program for information about screening children for parents and for professionals. So, they describe this in detail and what their experience has been with this program. [Slide.]

Dr. Hirtz: We also heard from investigators in the CADRE program from one of the CDC centers who are involved in a research program to determine the best instruments and best methods to implement

early screening. They described their ongoing research efforts. [Slide.]

Dr. Hirtz: Dr. Cordero also told us about a recent meeting at the CDC, which was focused on developmental screening for all developmental disabilities in which there was discussion about what are the challenges, what are the barriers and goals, which is, of course, very similar to the issues for this Committee, although we are focused specifically on autism screening, but they certainly involve all the issues relating to developmental screening, and they are intertwined. [Slide.]

Dr. Hirtz: So we tried to list in our discussion, what are the most important obstacles to early screening. One question was, do we or do we not have the right instrument? It was thought that we do have at least adequate instruments at the moment. This is not something that should hold up a nationwide program. At the same time, new and improved methods are under testing and should continue to be tested. It was noted that the early screening is not just important for the services

issues and getting children into treatment therapies earlier, but it's also important for the progression of the research that is planned; that in order to do research on risk factors and outcome and natural history, that early identification is one of the most critical issues and components of a research program as well. It may be that the paradigm for early identification changes as new information from science emerges, for example, for early biomarkers or biomarkers for autism that could be diagnosed, maybe even as early as after birth. That would certainly make it simpler. [Slide.]

Dr. Hirtz: Then discussion focused on how is it that we can best reach and inform the practitioners who will be doing the early screening. That includes primary care pediatricians, family practitioners, nurse practitioners, and the families themselves, who can also refer themselves for early screening. Some examples were given, such as the initiative of the American Academy of Pediatrics. It's actually called a Medical Home for upgrading

community services. This is, for instance, an existing network which could be used for propagation of information about early screening. There are different other kinds of activities that were mentioned and discussed as ways in which to communicate effectively, the need for early screening. Some of them are listed here, including something like existing federal agencies such as the Interagency Council on Infant and Toddler Programs. We even discussed whether perhaps the Surgeon General, current or recent past, might want to mount a public information campaign, as they have done before on other issues. [Slide.]

Dr. Hirtz: We discussed obstacles to the clinic- or office-based screening procedures such as time. Who does it? Who can do it? Are they trained? Obviously, the physician's time in a busy practice is very, very limited, and physicians are very resistant to taking on anything that will require more time, even if they think that they need to do it and should do it. So how do you overcome these sorts of obstacles? A third one that's tied into the time issue is the

reimbursement issue. If there's no reimbursement for doing the screening, it's really hard to make people spend the time. [Slide.]

Dr. Hirtz: And then what happens beyond the Level I screening? What's next? After a child is referred to the next level of screening, what do practitioners do? That may be an obstacle as to how or where they can send the children for referral and the fact that if there's a long wait for a specific diagnosis. When these children are identified as having problems, services should not wait. What are the ways to establish referral systems before even the final diagnoses are made, especially considering that there is clearly a bottleneck in the manpower for people who are expert in making a diagnosis of autism, and the training curve and the learning curve is a long one. [Slide.]

Dr. Hirtz: We also emphasized and discussed how different approaches are needed for different contexts. All health care in this country is not the same; there is an issue with minority populations getting access to screening;

healthcare is different in rural populations, and everyone who is involved, all the stakeholders, need to be involved in this initiative. [Slide.]

Dr. Hirtz: We discussed trying to find examples, successful examples of campaigns to change medical practice. These were some of the ones that came to mind, and we will explore and be happy to take suggestions for others. I was involved in some of the early Back- to-Sleep Campaign efforts and I know that was a tremendously successful effort. It's somewhat analogous, but, of course, not exactly the same, but that was a good example of a very widespread and rapid change in medical practice. [Slide.]

Dr. Hirtz: I just want to now spend a little bit of time on the recommendations and future steps that came out of this meeting yesterday, so one is that we do have adequate tools, but research and development of better tools, refining these tools, needs to be ongoing. A broad campaign needs to be put in place for publicizing, for informing, for teaching those who would be involved in early screening and the families. And

that campaign will need to involve education on all different levels -- marketing and some measure of quality assurance, both for the campaign and for the results of the campaign and what kind of change it's able to effect. There are a number of specific obstacles that need to be addressed, such as the supply of trained personnel, the issues of time and reimbursement. Suggestions were made for utilizing nurses and nurse practitioners to administer parent questionnaires. There are ways to address some of these obstacles. There's a need to involve all the stakeholders and to tailor approaches individually to the given situation of the family and the healthcare system. The Subcommittee will continue to promote and explore implementation of these goals. [Slide.]

Dr. Hirtz: It's not enough to just kind of say, well, here are some recommendations; see you in six months. The question is, what are the next steps? The Committee will continue to work to be very specific in drawing up a plan that delineates the following components: The target audience, what exactly and precisely would be the components

for a campaign, a public information campaign. And, very importantly, just distributing the information and getting screening in place is not enough, if that screening is not linked to referrals and to services. So, how to do that has to be part of the plan. We need to develop a very specific timeline and a method for evaluation of the procedures that are put in place. Now, I would like to open up the floor, specifically to comments from Dr. Cordero and other members of the Subcommittee, because I know I haven't covered everything that's important. I'd like them to add a little bit to this, and then we can take some questions.

Dr. Cordero: I think you did a very good job in presenting the key points that came out of the meeting. I think that my sort of overall comment is that part of what emerged from the discussion is that we're talking about a major change in terms of how the practice of, I would say, pediatrics needs to happen, some major changes in that practice. Basically, at the end, we're talking about every child having some form of

developmental screening, which has really not happened. If it's recommended by the Academy of Pediatrics -- and part of the reason is there are a number of barriers. And this is not only an issue in terms of the office and community; it's a issue for almost every condition, whether it's mental retardation, whether it's -- you name it, so there is a general need of having first phase screening that could identify the child that may have some development issues, and then have the more specific tests and start sorting out whether this is autism, this is cerebral palsy, attention deficit disorder, et cetera.

Dr. Insel: Comments from other members of the Committee?

Dr. Hirtz: Dr. Hanson?

Dr. Hanson: I just think it's useful to emphasize how this paradigm might change in the next five years, if we have some biomarkers to put in place, to go from a behavioral screening instrument, which may be difficult to teach people to use, to using something that a lot of practitioners are familiar with, could really

change this rather dramatically. The other issue is, what are the research agendas that we should be pursuing while we're doing this and in conjunction with this, so that research on the sensitivity or specificity of this and other kinds of screening instruments, research on systems, so that know how it gets integrated and whether it works or not -- research on topics like how do we change the behaviors of healthcare professionals and parents to promote these kinds of objections, and research on whether it makes a difference in the long run, that is, effectiveness.

Dr. Insel: Just to follow up on that comment, your report suggested that the screening that's currently there, the tools are adequate; the question is whether they are, in fact, accurate. What's the false positive rate for the screening instruments that we currently have?

Dr. Cordero: There was some discussion of that.

Dr. Doherty: The instruments that exist do have calculated sensitivities and specificities, not on a population base, so one of the things

that I think really needs to happen before this can be implemented broadly -- or maybe in conjunction with implementing it broadly -- is to look at a number of different combinations of screeners to see what yields the most accurate prediction in the end. If there's a lot of work to be done, there are tools out there that haven't been well researched, particularly in this country.

Mr. Shestack: There actually are population-based tools, but the sense of this Committee was that it's a very pressing problem to do the screening for kids with autism. Nobody felt that we want to wait until we have the perfect instrument in order to implement the plan and try to get Secretary Thompson to pay for it. What I thought was great about this group was the recognition that whatever came out of it was going to have to be flexible, would change. If there are biomarkers, for instance, it changes totally overnight. But what was important was that it be done quickly; that we try and come up with a proposal that could become a policy quickly.

Everything that they are talking about is not very expensive, as we all know. And it's certainly worth it. We all know that the first step to treatment is diagnosis and creating these materials and distributing them nationally. It isn't just roughing it out; it's $2 to $4 million a year; it's not very much. A physician education plan, patient and physician education plan was very specifically mandated in the authorizing legislation, and I think it's incumbent on us to get it going fast, even if it's not perfect. There is a group, a committee here that can be expanded, that can always be evaluating its effectiveness and refining it. And it seems like there's a real need for it now and it could do some good at almost any level.

Dr. Insel: Rick?

Dr. Rollens: I want to thank the Committee for taking on this important subject. Again, I'll share with you some experiences that we're having in Sacramento, and also my own personal take on this. Clearly, this is an issue that is going to need very extensive public/private partnership

between organizations like the AAP and government agencies like the CDC to do this. Keep in mind that our first line of knowledge about a child is from the parents, and I think that starts right at birth. So anything we can do from the day the child is born from then on, to sort of educate parents right away for certain signs of developing autism would be an important step forward. One of the things that we're doing in Sacramento is, in every doctor's office, in every little nook in doctors' offices where parents wait to see their doctors, we have a poster up there with a picture of a child up there and questions. If your child is not pointing, we all know the signs and symptoms and so forth. Please mention this to your doctor. It has been very effective. It's one of those things where parents usually have to wait in a doctor's office for a while to see the doctor. You can't miss this poster, and it's not very expensive to do, and we've found that a lot of parents, again, when they are just notified of things to look for, many times they will point it out to the doctor as, by the way, Johnny isn't

talking, Johnny isn't pointing or whatever. That's been very specific. I would also urge you to look more at bringing in a wide variety of developmental disabilities, not just autism. I say that because I think we can enlist a lot more support from other various organizations. We all want to know, if we are parents, what's wrong with our child, if it's autism or any of the other neurological disorders we're all aware of. Thank you.

Dr. Insel: Thank you. Other comments?

Dr. Alsopp: That was a nice segue into a point I was make, and the point I was going to make is, the practice parameter that was a policy statement that was done by the AAP Committee on Children with Disabilities, we made the point that pediatricians need to listen to parents. So, in addition to these efforts where we screen every child, there's a very important message, which is parents suspect that there is something wrong, or they know there's something wrong, and if pediatricians and other physicians and healthcare providers would listen, I think we would do a lot

to promote the identification of these children at younger ages. The other point is that I notice that you didn't have a representative from the Department of Education on your Subcommittee, or maybe I missed that. I just want to put in a plug for Part C. So even before a child has a diagnosis that these children can be referred for early intervention services, and at that point, the child can start receiving services, even if the diagnosis hasn't been clearly defined at that point. There's a lot that we can do in addition to the recommendations that are already there, to make sure that these children get identified as early as possible and get the appropriate services.

Mr. Grossman: I was just wondering if there is any consideration by the Committee of just some hard core marketing efforts in public awareness. It seems as though there are a number of disorders or diseases that are now being detected more readily, just through public awareness campaigns, either through advocacy groups or even private and government agencies. Has there been any thought

given to that, and, if so, what; and if not, why not?

Dr. Hirtz: I think that clearly that was part of what we were talking about in terms of how do we disseminate the information? One option I mentioned was the Surgeon General, but that's part of the different examples of ways to mount a public information campaign. And that's clearly one of the objectives. I completely agree with reaching the parents, but we also hear that parents will say, you know, my child's not talking or not pointing, and the pediatricians or doctors will say, don't worry; he'll grow out of it; just wait another year or two. So, we have to get all of the aspects. We have to get the doctors, the nurse practitioners, and the parents. Clearly, that's a major public information campaign, and it's clearly doable.

Ms. Chase: I'm a parent of a child with autism. Your first information as a parent that you get is when you're leaving the hospital, they hand you a little booklet. SIDS is something that's mentioned in there. I remember being scared

to death. I had read about it ahead of time, and suddenly it was in my packet, and it -- I had to make sure my child was fine. But what's happened is, there was some type of developmental sheet and a fact sheet, talking about not only autism, but the various developmental disabilities that can occur. Prior to even visiting the pediatrician for the first time, the parent has that information sheet, and have a checklist of things to go through, month after month. And then they are more of an informed parent. I know that when my child first had symptoms, I had no idea what autism was. Then I heard the word, and I was too scared to find anything out about it. However, if I would have known about it at any time -- I did have a developmental study done my children from birth to 18 or 20 months old. I was able to go backwards from that, and was then aware of the various developmental disabilities. They can go to their doctor and not only say I think, they can say, you know what? I have a pretty strong conclusion that this is what my child has. Then the doctor, that's maybe not informed, or the doctor that doesn't

have time to fill out a sheet like that, has the fact sheet in front of them already, and they can go back through their records. That was my suggestion.

Dr. Insel: Time for one more question.

Dr. Zeph: That approach is actually quite effective. I used it a number of years ago during early intervention with rural families. I finally gave them summaries and instruments, so that they could be watching for the normal development of their child or the lack of normal development, and bring those markers, those developmental milestones to the attention of their pediatricians. At that point, we were seeing for children -- at that point, for children who had hearing impairments, there was a two-year gap, an average two-year gap between the time the parent had assumed there was a problem or suspected there was a problem, and the point at which intervention was happening. One of the reasons I did this was just to give the power to the parent, so that they had something to show their pediatrician, so that they would be able to say, well, how do you

explain this? Or, help me with this; I don't understand. And they had something more tangible than "I think." Forearmed, I think that's an approach from the hospital perspective, when families are leaving the hospital, or if you state has Well Baby follow-ups for every child. At that point, if there is a visiting nurse program or whatever, that that be introduced very early on. The pediatricians' first concern was not to scare families. Families don't understand that this is an average that they don't want to over- identify or have a lot of false positives. But I think it's easier to tell a family that there is no problem later, than to say that they missed something. I really think that idea may be a really viable one.

Dr. Insel: Thank you for your comments. It reminds me that a two-year lag in therapy here has tremendous consequences, so this is really a key issue for us to stay focused on. I appreciate the inputs of everyone on the Committee, and those who gave their suggestions as well. Steve?

Dr. Foote: Before we move on, could I just ask briefly, what next steps the Committee thought

were most important at this time? I mean, there's a process issue here of having gotten an initial take on this problem. What I think I heard was a diversity of activities that could possibly be undertaken, but unless we somehow -- and maybe it's simple to say the Subcommittee is going to meet again and go over this again, but we need to figure out what the process is for consolidating and prioritizing and making some selection among these possible activities in order not to lose momentum here. So I'd like to hear the Subcommittee's comments on that.

Dr. Hirtz: Certainly we do agree with you, and do not intend to lose the momentum. I think the summary of what I presented to you is kind of the agreement that these are all priorities, and they're linked. It's very hard to say, you know, we will work on dissemination of information and not work on linking that to referrals and services; it really does come as a package. We do have to explore mechanisms to implement this, but I think the next step is a very formal and very specific report from the Committee and decisions

need to be made about who is going to do this and how they can get it done. The one thing we would like to do is make sure that we don't just kind of leave this report to dangle somewhere, but that the Committee is actually responsible for what happens in these areas, and that we would like to assume that responsibility and supervise and monitor what efforts we are able to put in place. And so I think that's actually really key. Maybe we can end on that note and move forward as we think about how the Subcommittees are going to function. The idea of you providing us some action items, and then us going back to you and asking how you're going to make sure that they happen, is how we go from this being a group that talks about the problems, to actually having some impact. I think that was the original charge, really, of the Child Health Act, and something that we need to keep in the forefront here. This really ought to be a way to make things happen, not just to discuss them.

Mr. Shestack: There's a meeting in six months. Obviously, the plan of this Committee is that way

before that meeting, through e-mail and phones, to actually have a draft of what this Committee would think would be a good implementation plan with the timeline evaluation and preliminary budget, and then we can feel how we can get it into operation, but significantly before the next meeting, we will have a draft of what the possible plan and implementation is, and take it from there.

Dr. Insel: Go for it, great. We're going to move along. The next session here is a report on the NRC recommendations regarding educating children with autism and the Center for Training Children with Autism Spectrum Disorders. Dr. Houle, from the Office of Special Education Programs in the U.S. Department of Education will provide that report.

Dr. Houle: Good afternoon. I'm bringing you greetings from the Assistant Secretary. I've done PowerPoint, but I have never managed it myself from the podium before, so I might need a little help. [Slide.]

Dr. Houle: Not this past Summer, but the Summer before that, July of 2001 -- I do bring you

greetings from Bob Pasternak, who is speaking at a conferences at our Centers on Dispute Resolution today, so, unfortunately, he couldn't be here. July 2001, we were very happy to report that the National Academy of Sciences has finished a two-year study that we had commissioned them to do. As you probably know, they don't do their own research, but they synthesize research bases. And what we in the Office of Special Education have asked them to do was to synthesize the research base on educating children with autism from and educational viewpoint. They pulled together a study group or committee of people with national expertise, and did a thorough analysis, had numerous meetings, with and without the funding agents, and in the end, came up with what we thought was a really on-target task report. Some of you may have seen this. I know Lee's group has adopted it as a statement for use with parents. Lee, your group was using this report on autism.

Dr. Goodman: We've adopted that as our position on educating children with autism.

Dr. Houle: Very good, much stronger. One of the things we were really happy about -- and this is a segue form Lucille's comment, was that this did give parents a tool, and advocacy tool, so that when they went into their IAP or IFSP meeting, they were not only the only voice saying that my child has autism and a significant disability and it requires a significant commitment of intervention resources to make progress. But they also had some documentation from the literature on educating children by the National Academy of Sciences. This is available on the National Academy website, and also it can be ordered at the www.nap.edu, the National Academy Press website. One of the salient recommendations from that report had to do with the training and professional development of personnel to work with children with autism in the schools and at the next preschool and infant level. There was a feeling that the dearth of qualified personnel is one of the major stumbling blocks and impediments to ultimately children with autism making progress. There has to be the commitment of

resources, and there has to be the capacity of resources to be able to fulfill that commitment. So, we have, I think, four federal agencies. It didn't take us too long to get out a funding priority, which resulted in the Professional Development in Autism Center. The funding is to start in January of 2003. We're funding it at $1 million a year for five years. The purpose of the Center is to provide technical assistance and training to service providers in the field, either directly or through their local school districts, through their local service provision program, or through their state education agency. My first commission to this grantee was to develop a PowerPoint presentation by November 22nd, so I will be able to bring this to present to you. So, Ilene Schwartz, who is the principal investigator at the Center of the University of Washington, which will begin in January, has kindly provided me with this PowerPoint for you. [Slide.] Bob could not be here in person. But if he were here, he might say successful implementation of IDEA is perhaps the most critically dependent on the

quality of the people who implement the principles contained in the law. That is, the teachers, the para-educators, related service providers and administrators in cooperation with parents and students. [Slide.] The overall goal of this center is to conduct the training across the country so that every student with ASD can access high quality, evidenced based educational services in his or her local school district. [Slide.] The need for this center was apparent, and it's apparent to every superintendent of every school district. It's apparent to most parents whose children are receiving either early intervention or school services. It was apparent to the Committee at the National Academy that the number of students with autism is increasing dramatically, and while we don't do the prevalence and incidence data, we do get data on the number of children who are being served under the special education category as autistic or autism spectrum disorders. [Slide.] Many models of service delivery yield trivial outcome. That was the synthesis of Sally Rogers' work reported in the

National Academy of Sciences report. I'm not prepared to go into all of Sally Rogers' work in that synthesis right now, but the technology and skills necessary to implement sound programming is not widespread. That is an understatement. [Slide.] The science related to effective practices is expanding rapidly, not always accessible, and is often at odds with practices in general education. While the numbers of children identified with ASD are increasing, the numbers of highly skilled personnel are not. Some of the strategies that are effective with children with ASD are relatively complex and really demand a highly trained level of professional expertise or expertise. [Slide.] The center is located at the University of Washington. They have co-PIs in the following locations. We'll get into that a little bit more here. [Slide.] The PI has the asterisk for each center and these are representative of universities of child development centers and of parent advocacy consortia. [Slide.] The guiding principles of the center are that children with ASD are children first and have the same basic

needs as typically developing children in many ways. There is no single right way to educate a child with ASD. Children are individuals, and child and family characteristics must be considered in intervention planning which, you know, a lot of it is contextual. If there's one thing that was learned about interventions and intervention testing and intervention staging and implementation is that a lot of it contextual. Knowledge is power. One of the most effective techniques for empowering families is to provide them with accurate information. That is the main goal of OSEP. It's the main goal of things that we fund such as the NAS report and this Center. [Slide.] All interventions must be built on evidence-based practices and must include ongoing data collection and evaluation. This is what the center will do. They're going to be responsible for bringing their investigators together and administering the criteria for anything that they disseminate or that is on their Web site that they see built on evidence-based practices. Effective interventions must be comprehensive and of

sufficient intensity to yield educationally meaningful outcomes. That again, this is work that is based on our investment in the National Academy of Sciences report based on the conclusions in the report which actually do talk about the number of hours and the labor intensity and resource intensity that is necessary in intervention for children with significant impairments due to autism. Training of personnel is best conducted in an ecologically and socially valid setting, utilizing aspects of adult learning and providing ongoing follow-up and consultation. I'll tell you a little bit more how this will be operationalized, or we may get to it on the slide. [Slide.] Comprehensive training must include teams who participate in role specific and trans-disciplinary training. It must be individualized. Effective dissemination must include different types of activities, formats and materials to meet the needs of different consumers. To that extent, one of the partners here, the University of Kansas, already has a distance learning center in special education up and operational. So that will

be utilized to disseminate and to train in the most effective distance learning techniques available to teachers and school service providers. Just as intervention strategies need to be evidenced-based, so do all training and dissemination efforts associated with this center. That's one thing we've been doing for a while. In our earlier centers, we actually funded a component of every research center to do some research on the dissemination of the knowledge base and information the center produced, so we can then take dissemination a level further. I mean, a professional journal and publication is important, but it's not the way everybody gets the information that they need. [Slide.] The strategic plan for this center -- and this is how we will operationalize individualized team training. By "individualized", I mean a school district might fund a team. A state might find a team or several teams. They may request a training of the trainer kind of model whereby the center will train a state team who will then go out and train local teams. Parents will be invited to be included in

all the training teams as well, to the extent that they are willing and able to do that. Exposing district teams to a broad array of empirically based teaching practices rather than selling wholesale name brand models of service delivery. We, was you know, if you're at all familiar with the Department of Education, really are trying to pick out and package the empirically based, soundest intervention principles from the whole array of models of service deliveries that are out there, as opposed to picking up one particular brand name and marketing that, because we do believe in individualized education for children with disabilities. Providing families with easy-to-use tools that will help them to make unbiased judgments about the empirical strength of proposed strategies and how plans fit with the family needs and strengths. [Slide.] Then district teams. Say a school district sends a team. They would be provided with empirically validated strategies, the competency to reliably assess the intervention that they're going back and implementing for children and families and alternatives, should the

intervention outcomes fall short of expectations. School district teams will be taught to design and deliver educational plans that are comprehensive in development and curricular domain coverage, and of sufficient intensity to yield meaningful outcomes. This is testing. This center is putting into practice what is said in this report, intensity matters. Age of intervention matters. Intensity matters. There are some principles in intervention that really have been proven to make a difference if practiced. Members provide district team members with the opportunities to see practices delivered in settings like theirs, and providing opportunities for them to actually practice strategies with guided support and follow-up. Throughout the country, principal investigators may oversee training that is on site for state school district or early intervention programs. So they will actually do some traveling to sites. [Slide.] Training for educational teams and parents that is experiential, site-based and ongoing, have used literature that are applicable for students from the age of diagnosis through 21

and incorporate diverse educational models. One of the modes of practice that they're going to use and how they set it up is that because they have this report as a jumping off point, they are going to in the first year update the synthesis of the knowledge base and begin offering training for working with children birth through age eight. During that time, they are going to be synthesizing the intervention knowledge base for the next older age group of children and add that training to the training menu that's available and continue on through age 21, which is the age that the Individuals with Disabilities Education Act under which they are funded ceases to be the service delivery mode. A Web site they will have the provides basic classes and information, even if it links to the distance learning, which I see that it probably will, and serves as a clearinghouse for training opportunities and provides interactive follow-up support for trainees. We made it very clear to the grantee that what we were not interested in is actually funding dissemination of the co-PI's individual

work. It's fine. You know, that will be part of it, but we're also expecting them to serve as kind of a refereed clearinghouse to make a lot of information that has been screened for quality available to parents, families, teachers, educators, the public in general through their web-site linkages and also in their training. Capacity building activities, including participation in ongoing summer institutes and leadership symposia, a diverse and active National Advisory Board. Now the site-based training process. [Slide.] How if you are from a state or you're from a school district -- and believe me, being in the Department of Education, the demand is high. We are getting calls all the time from school districts to bring them in -- state education agencies, early intervention programs wanting the availability of training. So the center will recruit participants and match them with the staff throughout the United States on needs, interest and geography, and some of that will be age range. We have people on the staff of this Institute who are experts in adolescence.

Some are experts in early intervention. Some are experts with school age children. They will start out with online classes on the basics. Then the center staff will go out to the training sites where the implementation will actually occur and local school districts will compete, to the extent that we have money, we can keep putting money into the center to broaden the scope and the service that they're able to provide, and they'll get a short-term internship at the center or intensive training at their own site. Center staff complete follow-up visits and then they can also use technology to follow up. [Slide.] We can use model demonstration sites. We can use the participants' own programs. The participants get grounded within their context for training, and that's basically what we're saying here. It's individualized and it's contextual. [Slide.] Evidence-based practice throughout the age range that IDEA is responsible for. They'll also be doing topical areas on their Web site and documents for diverse audiences. [Slide.] This is what we expect out of their Web site. [Slide.] This would be some of their basic

classes that people would have a basic understanding level before they go in for the intervention training. [Slide.] Some of the benefits of having a broad Web site is that you can offer these services through Web and consultation. [Slide.] These are some of their capacity-building activities. [Slide.] The National Advisory Board. This is who they'll be looking for as representatives to serve on the National Advisory Board to get connected. [Slide.] And this will be officially starting January 1, 2003. The other I brought, and I won't go over it, I will only hand it out, is a summary, the study directorate NAS and I prepared at the close of the study, where we provided information to others at the National Academy. This summarizes that book that I was holding up and the report in terms of the salient recommendations. So I have copies of this. And hopefully if we run out, we can get more copies. It is a little aberrant. You'll notice it's folded over with page 1 here. I had somebody Xerox these for me at the last minute last night just doing it like that and I didn't realize it

was starting with page 2 and page 1 was on the back. So the best laid plans. How would you like me to disseminate these? Should I do it right now? Thank you so much. I'm finished.

Dr. Insel: While those are going around, are there comments or questions about the report? [No response.]

Dr. Cordero: Gail, thank you for a very nice presentation. I have two questions. One is, how do you see the coordination with the sort of non-educational groups, for example, the children have therapists and physicians, pediatricians, developmental pediatricians and perhaps some perhaps some that may be taking some medications and so on? And how are the medical aspects of the management of children with autism combined with what you're planning on the educational side? The second question is more how this project is going to address the issues of diversity in terms of children that may be, say, Spanish speakers or of other cultural groups, say, Native Americans or African Americans and so on?

Dr. Houle: Because they have not yet started I can't give you answer that they are doing it or that they're going to do it exactly this way, but bringing that to my attention, one way that comes to mind will be of course representation on the National Advisory Board. That will be one of the first steps. That representative will be responsible for providing the input and kind of the monitoring, how well are you doing with your non-English-speaking population of parents. We have the resources and we have the Whole Parent Network that is very interested in translation and providing information and training. They will be required to have diverse representation on the training team that come in for training among the parent groups that they go out to meet with as well as the Advisory Board, and we have a network for translation of materials. We also have a network from a multi- cultural clearinghouse that we've been funding that where parents and professionals from different cultures and cultural and linguistic groups review material for appropriate sensitivity to the population that

they represent. So we already have that in place from other projects, and we intend to leverage that for the Institute as well. And the non-education aspects. We are doing work in that area. Rather than be redundant, it's always an area that we are continuing to work on collaboration with our Part C program, which is Infants and Toddlers, mandates in the statute that the health-related professionals, including physicians, be equal partners in service deliver and service design systems, and they're funded to do that. We are aware of it. I'm not saying we'll be perfect, but we have some experience that we can leverage, and we will expect our center to leverage.

Dr. Insel: One more comment before we go on.

Dr. Kallen: My name is Dr. Ron Kallen. I'm a pediatrician in Chicago. I'm also a parent. In general, my experience with special education is probably like many parents. I've never met a teacher who doesn't know about autism. They've taken the course, they've been to the conferences. That doesn't mean they're implementing the optimal practices. So the piece that I'm wondering about

in the PDA is, how do you then go back and do whatever it is, quality assessment or outcomes measures, accountability? The people have been trained. Are they really accomplishing what we as parents hope they will do? Is there an accountability piece to this?

Dr. Houle: You brought up two things. We're grappling with a couple of things. One is the teacher in the regular education system. The law mandates that they are responsible for the education of the children. They're not special ed children, but they're children within the school system, so they will be part of the team. The teams will be responsible for going back out to the sites. This is a model of service delivery. A million dollars a year is not enough to provide trained up teams for every child with autism, but we don't want to see it continue to have to say that we don't have access to models. So states and locals will have to put some money in too. And how do we follow it up at the local level? Certainly the resources are there, and it's going to be most successful in school systems and schools that put

some comparable training money into ensuring that the team can come out and follow up or designate one person in their school system as the leader. There are several models for doing this, but the infrastructure will be there. It's a matter also of the will to commit the local and state resources to this. If your child is in a school, there's nothing that would prevent your child's school district from sending a team for training, and there is nothing that would prevent you from going with that team to train. And there's nothing that would prevent your school district from putting resources into continually monitoring, providing data back to the site. They can send a couple of people from their team to go out and monitor if the interventions are not successful. This is a technical assistance center as well. But we can't do it all from a top- down federal center. We have to have the will and collaboration from the school districts and the states as well.

Dr. Insel: We'll have to move on, if I can interrupt. I think the point that he's making, which is something that we should continue to

include in the record, is that the outcome of such a venture needs to be studied very clearly so that you know what actually is working and whether it can be generalized or not. That's something that will be an important part of any of these programs.

Dr. Houle: Right. And for the most part, the university-based PIs have a history and skill in being able to do that. So that's part of it. So it's as much a TA and training center as it is a research center. We feel like there is somewhat of a knowledge base already, at least birth through 8. But the big salient call in this report was that there aren't enough trained people to implement it successfully and monitor it.

Dr. Insel: One thing we can do is to make sure that the URL for that report is on our Web site so at least people who want to access it can do that. A lot of work went into that original National Academy of Sciences report, and it's something we should all take advantage of. Thanks, Gail, for that very helpful summary. The next session is an update on the other subcommittee that was set up

at that last meeting. We heard about the Screening Subcommittee already, and as you remember, one of their points was developing the links to referrals and services after the screening is done. So logically, this is the other subcommittee to hear from, which is the Services Subcommittee. We've got a panel of people who will be talking about that subcommittee meeting. Do you have slides as well? And who is going to take the lead on this discussion?

Dr. McPherson: Let me just make a few comments as the co-chair. I want to thank NIH for acknowledging the need to have the service agencies as part of this coordinating committee and setting up this subcommittee. We're very pleased with that. I also want to acknowledge that it is being co-chaired from SMSA and HRSA to once again acknowledge at the service level the need to bring the mental health resources and the health resources programs together so that we are co-chairing it. [Slide.] The other thing, we are two agencies that have very extensive programs out there that are involved in developing the systems

of care for children and families that were part of the presidential initiative in building on the promises. But we also have no targeted dollars directed towards autism as part of that effort. So what we're doing is really talking about our generic efforts and looking at where to build things. The other thing we would like to do at the end of the session is to come back to this question about what the roles and responsibilities and the scope of work of the subcommittees are. As you'll recognize, the service systems out there are huge and need to be brought together. So we'd like some focus on that. We elected to bring people in from the field to talk to you rather than us talking to you, because there are so many diverse perspectives from the services, and I'm going to turn it to Lee to take the lead.

Mr. Grossman: This is actually a continuation of what was presented at the last IACC meeting in May. [Slide.] This is part of our approach on the subcommittee to introduce to you the very, very critical and very important aspects of having service delivery as part of a national way of

approaching the needs of the autism community. When IACC started about a year ago it was heavily dominated by the research end, which is extremely important, and I applaud this committee for opening itself up to also include the service sector as part of what needs to be done to address this problem that we have today. In the next hour we have four presenters who will have about ten minutes each to talk about what they're doing in their local communities to give you a flavor of the array of services that are working in the community as well as they're going to talk about the needs that they have going forward. In the time that will be left, which will be about 20 minutes, we're going to engage in a panel discussion where we'll be entertaining questions from everybody here as well as providing you maybe next steps in the process. [Slide.] I am briefly going to go over where we are today and also lay the groundwork for where service delivery fits into this autism problem. What we know today is what you see on the screen. I'm not going to go through the whole thing, in the interest of time.

There are a couple of things that need to be pointed out today. All the figures up here are conservative. They are conservative figures. Today in the United States, one in 250 births will develop autism. The significance in that is not only what we have today, but that means in 20 years that one in 250 people in the United States will be entering the adult service sector, which is virtually nonexistent today and is flooded and overwhelmed today. In 20 years, as you can imagine, we have to start doing something now to be able to address what will be a tsunami of people entering into the system. As you can also see from some of the figures here that we can significantly reduce the amount of the service costs through early diagnosis and early intensive intervention. And one of the other key statistics that I find here that are very telling is that 90 percent of the costs for services are in the adult sector. [Slide.] In synopsis, I Just want all of us to take away from the figures that were just presented is that this is national emergency. It's an economic and social crisis. [Slide.] And autism

is an epidemic. [Slide.] There are four critical needs in the autism community as they're stated here. And as you can see, research is one and the rest are really centered around the service delivery model. [Slide.] The realities of autism today that we're all dealing with are as presented here, which again bring together the aspect of services working together with research at all levels across the lifespan if we're going to deal with the realities of autism. [Slide.] I presented this at the May IACC meeting what the needs assessments are. Here you can see that the service array is vitally important if we're going to adequately address this. [Slide.] And what's needed from the federal government is a coordinated and aggressive response. This includes multiple agencies. The presentation I gave in May I broke down those four critical needs and identified at least from my position what agencies would best respond in those various needs. In the interest of time, I didn't include that, but that might be something we do send out on the Powerpoint slides. [Slide.] Also, in dealing with

the puzzle of autism, as you can see, everything is interrelated, interconnected to address the needs of the individual with autism. I'm next going to call up Dr. Cathy Pratt from Indiana, and I'm going to allow the panelists to do their own self-introductions. Thank you.

Dr. Pratt: I'm going to ask neither Lee nor Gail to help me with Powerpoint. I can make the mistakes on my own.

[Laughter.]

Dr. Pratt: [Slide.] I thought it was going to be appropriate coming from the state of Indiana where sports rule that there should be an athletic picture up there, although probably should be basketball. I come to you in multiple roles, one is as Director of the Indiana Resource Center for Autism at Indiana University, and we're part also of the network of the University Centers for Excellence and also a member of the Board of Directors for the Autism Society of America, and as a past classroom teacher. We are a statewide training and technical assistance program that has been doing many things that Gail has talked about

in her presentation. But I just wanted to kind of go over some of the concerns. [Slide.] And I know this is very different, because we're really talking about services and what we see in the field. One is is that I see a trend towards generalized certification, and as a result of that, really a lack of trained personnel. At the same time, I feel the need to say that some of the people who I think do some of the best jobs with children are not necessarily the ones who go through Autism 3000, but they are the ones who are just tremendously wonderful teachers. We also see that there's a number of individuals teaching with limited licenses, and the reality of that is that oftentimes those teachers are relegated to working with the kids who have the most significant disabilities, and they are the least trained. We also see that there are a large number of individuals being served in general education classes and settings and that most professionals who go into the field of general education never receive even a course on autism. And then untrained paraprofessionals are taking an

increasingly active role, and are often left to do a lot of the education without very much support. I also see as I travel around the state of Indiana and nationally, increasing parent frustration because of so many issues: The lack of coordinated services, the lack of resources, the lack of trained personnel. As a result of it, I also see increased fighting between schools and families that are kind of making sure that we give a lot more of our limited resources unfortunately to those issues, and decreasing funds during a time when students are becoming more complex. And having been in the field of autism since the seventies, what I see is the changing face of autism. These individuals are much more complex than they used to be in the seventies and eighties, and a lack of interagency support for these students who are complex. And when school districts feel they no longer can serve children, they are oftentimes sent to highly restrictive settings. [Slide.] So here are just some of the things that I see needed. [Slide.] Funding for research that focuses not on clinical approaches,

but on those approaches, strategies and program components that lead to the greatest outcomes for students. I guess that I'm a little biased, because having the opportunity to see individual's live span, to me, the outcome for individuals with autism is that they leave school and they are employable. I think that our greatest indicator of success will be that we have individuals with autism who have jobs, who live in the community, who are not living at poverty level. And Anne will be talking about some of these issues. But many of the individuals that I know who go on for advanced degrees even are living at or below poverty level and don't have jobs. So I hope that we will focus on some of those outcomes, and in addition to that, those practices that are evidence- based and result in those outcomes for folks. [Slide.] Unfortunately, oftentimes these types of things are being decided in courts and not in educators getting around the table and having discussions. And so I'm really glad to see this effort from the Department of Education to put together a group of people to look at some of these practices.

[Slide.] Being that I work at a university, I realize that there is a responsibility for those of us who are in higher education. And I would encourage this Committee also to kind of reach out their arms to those individuals who deal with higher education to look at how we prepare both general and special educators for the realities of dealing with these incredibly and increasingly complex students. [Slide.] And if there is a certification program, and I know that in some states parents are crying for teachers certified in autism, that it's not used as a means to exclude students from the least restrictive environment, which is what I see happening in some places in our country. [Slide.] If paraprofessionals are going to take a more active role, we have to put funds behind an effort and training behind training paraprofessionals so that they are really qualified and prepared to be doing the frontline work with our individuals. And perhaps there needs to be licensing procedures. [Slide.] Again, since many of our folks are living at poverty level or are unemployed, there needs to

be a more aggressive approach to preparing individuals for jobs, and there needs to be a very definite linking to adult services very early on. I know that that has also been an important part of the Department of Education. [Slide.] And so the personnel really need to be trained to better facilitate this transition process. Too often I see it happening where there is not a discussion held until the individual is 21 or so. [Slide.] Along with that, rather than just the one- shot training, we actually in Indiana have trained 180 teams in our state. Those teams consist of superintendents, principals. We've had bus drivers that have been trained, general special education folks, parents, a whole host of people that we bring together for training and then provide ongoing support for. But in addition that, what I see is really a need for a kind of cohesive state and regionalized personnel preparation programs. What we are finding in our state is that what is highly effective is if school districts actually hire autism coaches or mentors. Because the reality of it is, is that oftentimes people

receive a lot of training, but when they close the doors of their classrooms, they need ongoing supports to be able to implement those practices. So coaching needs to be available for those folks to be able to do their job effectively. [Slide.] We also need to have an expanded focus on intervention at the zero to three level. And unfortunately, too often, heavy services kick in when children hit the age of three, and we really need to be focusing earlier on kids. And that means that those providers need training. In some areas of the country, people who provide services to zero to three are not very well trained in providing services for young children. And oftentimes those services are not very integrated or coordinated for those children. [Slide.] When the educational system is unable to successfully educate these children, other agencies need to be willing and funded to step up and provide additional assistance. Another one of the members that I hope we start seeing at the table are people involved in the criminal justice system. Unfortunately, I am receiving phone calls from

families of children as young as five or six or seven or eight. And Jamie from TASH, you can probably talk about this, but children whose behaviors are being misinterpreted, and they are already getting in trouble with the court systems. And the courts are unprepared and uneducated about how to support these individuals. We also find that because of the complexity of these children, that oftentimes in addition to autism, they come to us with mental health issues. And the mental health community and educational community has to partner around these children. About six months ago I had the opportunity to speak at a conference, LRP, which is kind of the legal conference for special educators. One of the cries from the local directors of special education was the need for interagency agreements with all the agencies in their community to really partner up to come around these complex kids. Because the reality of it is that right now these kids, when the educational system can no longer support them, we are now looking for institutional places, places in the criminal justice system, and these

kids are failing dramatically. It is these kids who have tremendous potential but because of us not being coordinated in our efforts are really failing. [Slide.] Statewide parent training and resource centers. I hear from families when they first get the diagnosis, and oftentimes they call me and they say, how do we make sure that we don't mess our children up? How do we do the very best for our children? So we need to be there not just in major cities but in urban areas, in rural areas, and looking at families who have limited abilities themselves and also making sure that we're hitting minority populations, which are oftentimes underserved. [Slide.] Families need advocates who will help them interpret the system and negotiate the maze of services in a positive fashion. They will have to be interpreters of what's going on and help them to understand how the agencies come together. All of us work as separate agencies. They are dealing with one child. [Slide.] In addition to that, families need access to additional funding and support that allows them to supplement their children's school

program. Earlier, Merle, you talked about the fact that many of these children and their families lose insurance coverage when their child is diagnosed with autism. That is a very great issue for a lot of issues. [Slide.] And families need access to affordable and readily available training that will provide them with the tools to be able to effectively support their children. [Slide.] Currently there are efforts that are going on, and I hope that we don't duplicate efforts that are already happening. The Autism Society of America has for the last several years had a group of folks that are part of a nationwide network of training and technical assistance programs that can provide a mechanism for cohesive research, personnel preparation and training. We do a lot of training with physicians. We go out and spend a lot of time in the community and some of the states involved in that. [Slide.] In addition to that, since Indiana University, the Indiana Institute is part of AUCD, I would really encourage that you look at that group also, because that is a mechanism, and what we do in

every state is provide training, and it's a really good, coherent, cohesive kind of organization that can do some of these things. Okay.

Dr. Holmes: I'm Anne Holmes, the Director of Outreach and Support Services for the Eden Family of Services. Eden is somewhat of a unique program. It's a private, nonprofit agency that serves individuals with autism, basically birth to death. We have an infant and toddler program. Right now we seem to average about 3,500 three-year-olds at any given time. Our youngest is a 9-month- old. It's a sibling whom we're watching, which we have done for many families. We've been able to watch some siblings where the parents are concerned. We have a school-based program which serves 50 students from three to 21. Then we have quite a large adult program. Currently we have 10 group homes in the community where six of our adults live. We have three employment centers where 85 of our adults go. They are focused for employment, and I'm very proud to say that 100 percent of our adults receive paychecks, some very, very small, some enough that make their job coaches jealous.

So it's a nice problem that we have. I have the privilege of just in a short time to focus on this adults with autism. Thinking about the definition of autism, the third word is lifelong disability. I think we don't think enough about the adults. It seems at 21 they really do fall off the face of the earth. If you think about it, trying to do some rough statistics, but we're all going to spend about 75 percent of our lives as adults, maybe 60 years as adults. Right now I'm thinking that we'll give into the 80s, and with autism it's really good news. When I started in the field 26 years ago, the leading cause of death in autism was choking to death in institutions because of overmedication. That's not an issue anymore. Our adults with autism should live normal lifespans. So we're going to have, as Lee said, we're going to have a significant number of adults in that area as time goes on. Every year at 21, there's a new bunch of adults with autism needing services. Cathy alluded to individuals who maybe had gone through high school and secured a job, and the school system worked quite hard at getting that.

The hope is that this will somehow continue. I've sat on enough teams where, well, they'll just continue, individuals with autism that are quite high functioning can continue for a while, but often they fail because there are no supports. These individuals have gone to colleges, Cathy said, and can't get a job after that because of the real challenge to their social skills, and just keeping and maintaining a job. Then you have those that are more involved, those that have many more issues, which tend to be the individuals which we serve at Eden. We have had the pleasure of deinstitutionalizing half of our residents out of our state institutions. They have taught myself and our staff more about learning and about what adults need. Elizabeth Gould, who is a researcher at Princeton University, last spring, published her study on aging primates. And basically, what her research said is that aging primates, if stimulated, develop new neural pathways. We took the jump just mentally and said okay, if primates can develop new neural pathways from stimulation, absolutely our adults with autism can learn with

stimulation and with programming. This has I know for us been such a kick to say that learning doesn't stop at 21. In terms of service delivery it does, because we're challenged with no entitlements and no funding for programs. Most adults with autism are probably right now at home or in a state institution. We get called in often to look at an individual in a state institution. They want to know about diagnosis, and our team will go in. One hundred percent of the time we share with them, do you realize that half the other young men and women sitting in this room also have autism? So their mouths drop. Our institutions are filled with adults with autism, also in their home, their home with aging parents, their home with parents that are tired and have every right to be tired. As we always say at Eden, autism never sleeps, literally and figuratively. So you have the challenge of these parents trying to maintain these kids at home with no services. Some of the challenges, and there are many that face the adults with autism and service providers, one is just trying to interest specialization in

adults services and providing these services for adults with autism. Adults with autism, although parents and staff think they're cute, they're not cute. At 50 if they have a tantrum, it's not cute. There is not a desire for service providers to go into that field of residential services and adult services for autism. It's hard work. It's 24/7 as we say. On every holiday, the group homes are running, and it's been very difficult to get agencies to want to specialize. Adults with autism typically fail in your generic group homes and employment centers. They do not fit well with the mold in the population of mental retardation, cerebral palsy, you're looking at ratios of 40 to 1 for our population. They fail miserably. We have very few groups of individuals that want to provide those services. Another significant challenge we have in service provision for adults we have are workers. We provide extensive training, but at times when our economy is good, we are truly competing with McDonalds for staff. Those are the individuals, not just taking care of teaching our adults with autism 24/7. You know, as

I would say and my boss always says, you say to the parents, you know, mom, I'm going to go to school and I'm going to go to college and become a special educator, and your parents say that's great. Who goes to their mom and says, mom, I'm going to be a human service provider? I'm going to go work in a group home. We've got to professionalize that field. We have to have career tracks. And maybe they're in our county colleges where an individual can go and get a degree in human service provision, and then we have a pool to pull from, and that respect for that worker is just raised, which we need so significantly. Funding is an ongoing issue. The only reason why Eden can survive and offer our services is because we have an incredible fundraising division that supplements all of our funding. We have gotten zero percent increase from the state for several years now. And, you know, there isn't a zero percent in expenses. So we're looking at a serious funding issue. Another issue too that I think impacts -- we're talking about crossover agencies. The mental health issue came up, which is a

reality for adults with autism, just the whole medical care. Our population of adults, many of them have been on medications their whole life. We have a number of individuals right now that are suffering from serious liver issues and kidney issues because of medications their whole life. We've got those issues medically. We also have the challenge with autism that they can't tell you where it hurts. And it's so difficult to sit with a doctor and not be able -- you know something's wrong, but you can't say it because he's not going to grab the stomach here and the adult is not going to put his hand up here. So in terms of finding good medical care is an ongoing challenge. The issue that we struggle with, and I hope that all you will struggle with, is there are no entitlements for services for adults. So if there are no entitlements, money is not going to follow the entitlement. I would like to end. I have about two minutes. And it is a story because it's worth telling, a story about Larry, who was in the institution from when he was three to about 33. I'm not exactly sure how old he was when we were

able to take him out of the institution into our group home. He did nothing for those years, pretty much did nothing. All his records, I was reviewing his records, and he was nonverbal. All his records said he was nonverbal, and he pretty much was in the dayroom. And on his nights out, he would walk around the campus. We took Larry into our group home, and Larry is a big guy, so we very slowly took him off his medication, which was beyond a list you couldn't even imagine. It was every medication possible. Gradually took him off his medications, got a good balance of medications. Larry is verbal. Larry was just so drugged his whole life that he couldn't speak. Larry speaks. Not that he has huge conversations, but he definitely can tell us what he wants, what he doesn't want, where he wants to go. And he has a job, and he loves his group home, and he makes a paycheck. There are so many Larrys out there that I think if we can just pay attention to this end of the autism spectrum, we are really committing to that lifelong disability. Thank you.

Ms. Alfreds: I think our major accomplishment will be not destroying the audio/visual and technology of NIH. I will need the Powerpoint instruction. [Slide.] I'm Myra Alfreds. I'm the director of a public community children's mental health system in Westchester County, which is a county just north of New York City. We're about 923,000 people, about 200,000 kids under the age of 18, and I've been in the children's mental health field for about 14 years. I am also the project director for a children's mental health services grant and principal investigator and work with Columbia University Psychiatric Institute, and it's because of Sybil Goldman that I am here, and I said what do I know about autism? But I think what we're talking about here is children and families, and children also who come through a lot of different doors. [Slide.] Around three-and-a-half years ago as we were looking at children in the public mental health system, the majority of whom are using public services that come from a variety of systems, we noticed that about 20 percent of the children who were in the children's

mental health system also had co-occurring developmental disabilities, and we started to become very concerned that the families were coming forward but that the systems weren't necessarily coordinated and working together. We decided to do some looking together and analyzing what are the differences and what are the similarities in the system. I present this because these became some of our challenges in putting together a system that follows principles that I can highly recommend as organizing principles across systems. These are the child and adolescent service system principles. They are family-driven, individually strength-based, culturally competent, and I have yet to find a system that doesn't at least acknowledge that these are values and principles in their system as well. So it may be something that can bring people together. But we found, we are in New York State, that the developmental disabilities, which includes children with autism, is a state-driven system. The mental health system is a county-driven system. We have various services differences.

Children who have very serious behavioral issues, often who we find in psychiatric hospitals, need an intensive level of service that currently is only provided in the children's mental health system at a ratio of one case manager to eight families. The MR/DD system cannot replicate that. So these children are landing in the mental health system, and we are accepting them based on their mental health needs, but struggling very hard to serve them in a comprehensive way. We are finding that there is some difference in family support in our two systems. That is, in the MR/DD system, families are attached to programs. In the children's mental health system, we have a family movement that is separate and apart from any program, and these families find themselves in and out of all of these systems at any given time. So we want to try to work together with the MR/DD system to provide families what they need when they need it. You may be surprised to see that on the MR/DD side, we said many funded services, but when we looked at family support, recreation, community services, believe it or not, there is

much more available for kids with developmental disabilities in the communities than there are with kids with serious emotional problems. Again, we want to work together across these two systems to serve all of the children. We're finding in the MR/DD system, there is still a model of dispute resolution. Who does this child belong to? This doesn't always work well because there are many children that are between systems in gray areas that we want to come together. [Slide.] In Westchester County for the last 13 years we've had a model called Network. This is what it looks like. The child and family is in the center. They are in local communities, and together we are looking to engage all of the service systems. This works best when everybody can come with open hands and an open mind to really look at that individual child and family and puts their resources together on the table. We are now in Westchester County working at increasing numbers of very young children, children eight and under who are increasingly coming into emergency psychiatric services. In that population we are predicting

that, again, 20 percent are going to be children who have both mental health and developmental disabilities. These numbers are going up all of the time. We're looking for ways to come together across these two systems to serve these children. We are also looking at the other end of the spectrum in our kids who are now aging out, an even higher percentage of kids with developmental disabilities who have gravitated toward a system that has some peer support models. On the family support side and the peer support side, we're trying to have an open system to work across these two systems. [Slide.] What we have done in Westchester County so far that I believe is having some effect is that we are sitting together and have for the last three years in a cross-system planning group. We are looking through things like home and community-based services waivers to put together because that exists in both systems, and these are Medicaid waivers that states have available, that there are case managers in both of our systems, and yet there are children and families that need services at a high level of

case management. There could be work directed toward looking at Medicaid waivers as a way to bring together systems. We're doing it operationally. We would love federal support for this as well. We said even if we had all the money and all the services, we do not have a trained workforce. And last year we developed what seems to be the only cross-system training for workers in the mental health and developmental disabilities field. It's about 25 hours of training. People receive certificates that they've completed it, but we've found an inability in both of our systems to really understand how to work with these kids and families that have multiple challenges, and we are going to be repeating the training every year. We've contacted the National Association for the Dually Diagnosed to find out if there is and has been an emphasis on adults, almost nothing specific around children. We are really trying to encourage them to allow us at least to take some leadership in this and focus on the needs of children. Again, an advocacy issue with NADD to bring this to the forefront, and

dually diagnosed is mental health and developmental disabilities. As a result of training, again, we have searched through the United States to find that there really is not attention across these two systems on children. And as a result of our training, we've put together something of a resource book. Some of the challenges that I am thinking about, having attended this meeting, is we are missing an opportunity if we only think about screening with pediatricians and with medical people. What we found is, often the first people to enter these families are people from other systems. We're talking about child welfare workers. We're talking about other kinds of professionals. If we develop screening instruments, can I recommend that it goes broader than medical people? Because you are not always the first ones to know that there's a problem in the family. And I think that's all I'm going to say.

Dr. Noyes: Good afternoon. Can everybody hear me? My name is Donna Noyes. I'm the Director of Policy and Clinical Services for New York State's

Early Intervention Program. [Slide.] I'm here to talk to you today a little bit about our clinical practice guidelines for young children with autism, but I also want to start by telling you a little bit about Early Intervention. [Slide.] I'm sure that all of you know that Early Intervention is a national program under IDEA for children ages birth to three years with developmental delays and/or disabilities and their families, and the program provides for a broad range of evaluation, assessment and intervention services for children and families. [Slide.] In New York State, our Department of Health is the lead agency responsible for administration, financing and monitoring of the Early Intervention Program. We also have a very strong role for county governments. They're responsible for finding eligible children, developing IFSPs, contracting service providers and seeking reimbursement from third-party payers. The county governments actually share the cost of services with the state. [Slide.] Our mission at the program is to identify and evaluate as early as possible those

infants and toddlers whose health development are compromised and provide for appropriate intervention to improve child and family development. [Slide.] We as a Health Department have had a strong emphasis on early intervention in the medical home, a strong commitment to ensuring physician involvement in the Early Intervention program, surveillance of at-risk children in our Child Find efforts in IFSP monitoring of progress, and we have a number of activities to support that involvement, from medical home grants that was recently awarded to us, a strong parent involvement, committee of our Early Intervention Coordinating Council, and training and outreach program for physicians. [Slide.] I wanted to tell you a little bit about the scope of our Early Intervention Program in New York State. When we began in 1993, we had approximately 9,000 children receiving Early Intervention services in the first year of service delivery. We now in our most recent year with our current data have around 58,000 children and actually this year we're experiencing something

more in the neighborhood of 60,000 children and their families who are in our Early Intervention Program. And just to give you a sense of the cost, we're well over half a billion dollars at this point in service delivery expenses. Of these children, in 2000-2001, 519 were identified as having autism or pervasive developmental disorder with an actual diagnostic code. I would also say that when we look at the patterns of developmental delay status, it's probably true that there are another around 500 children just based on the pattern delay being cognition, communication and social and emotional delays. So that 519 is probably actually a bit of an under count. [Slide.] Our service delivery issues included obviously a high need population, parents seeking very intensive levels of early intervention services, a lot of questions from public officials, providers and families about what effective interventions are available. A real need for better data on our own service delivery system in terms of children with autism. A need to improve service delivery capacity, and obviously

funding is an issue. [Slide.] In 1997 we initiated a clinical practices guideline project to help us address some of these issues. The project in its total will actually result in six clinical practice guidelines. The first two guidelines that we tackled were autism and pervasive developmental disorders in part because of some of the issues I just addressed, and communication disorders, because obviously that's one of the most prevalent problems we find in Early Intervention. We also have completed clinical practice guidelines on Down's Syndrome, motor disorders, vision impairment and hearing loss. And these are all currently under our final review within the Department for release. [Slide.] We used an evidence-based methodology based on the Institutes of Medicine and the ARC methodology for development of medical practice guidelines. We had a project staff that included a methodologist and research teams, and we had six different multi-disciplinary consensus panels, all of which included parent consumers. And I just want to take a minute to say how important those parents were

on the panel. We actually were able to fund them to participate so they got a stipend that was comparable to the clinical and research experts who participated. We had four parents on the panel. The panel was chaired by a primary care physician from our Rochester area, and they were just really important to the effort in terms of helping us pinpoint the important issues for parents. [Slide.] We looked at 20 years of research. All of the panelists reviewed the evidence that met quality and clinical applicability criteria. We looked at studies that included children up to six years of age. We then had the panel develop consensus recommendations that would address their recommendations around practice issues related to assessment and treatment of children with autism. And we had a national and international peer review process. [Slide.] I wanted to tell you a little bit about the scope of our guidelines. They include a lot of discussion about developmental surveillance and screening and again, targeting physicians but also, as was mentioned earlier, the need to reach

other early childhood providers with information about autism. We looked at assessment and may have recommendations about assessment instruments, developmental assessments, and also health evaluations. We looked at the literature around MRI and SPECT and food allergies and diet assessment, and the guidelines include recommendations in those areas. [Slide.] The scope of the autism guideline related to interventions include general approach to intervention. Behavioral and educational approaches were among those found to be, based on the science that's available, the most effective for young children with autism. And we looked at what literature was available on intensity, and I would say across all six guidelines, the only place we found evidence on intensity was in the autism work, and the panel did recommend 20 hours a week, and also qualified that with factors that relate to individual child and family needs. [Slide.] We also addressed a number of other approaches, sensory integration. We found no evidence for any other approaches, at least in the science. The panel did recommend a

qualified use of sensory integration and the developmental model that's been developed by Dr. Greenspan. We couldn't find any evidence related to music therapy, touch therapy or auditory integration. And these were all areas that the parents felt very strongly we needed to address. [Slide.] In terms of the use of our guidelines and future plans, we have widely distributed our guidelines to our county officials, to physicians, to providers, to families. We have an ongoing program of training. Our plan is to update the guidelines as new evidence becomes available. And I would say with the autism guideline, that needs to happen relatively soon. There has been new research coming out that would I think impact on some of the recommendations. And we're considering strategies to evaluate the impact on the quality of care. I would just mention that I told you earlier that we had around 519 children in 2001 identified as having an autism. Prior to that, our early experience with Early Intervention, we had across a four-year period 77 children identified with that diagnosis. I don't think we were only

serving 77 children with autism, but I do think our efforts related to helping people recognize the importance of giving a diagnosis early has made a big difference. [Slide.] We are also in the process of developing standards and reimbursement rates for behavioral aides and paraprofessionals. This was raised as an issue, big issue for us in New York around capacity. [Slide.] And just to close, some recommendations that we would make is again, really the continued support for research is critical. And I would say services research is critical. That some of the issues that we are dealing with as states relate to the type and intensity of interventions that lead to good outcomes. I think the early identification area is very important too. And then I think it's really important to include state administrators and both early intervention and children with special health care needs administrators as target audiences for research. I'm very pleased to be here today. It was a wonderful experience for me to hear about the research, and I'd love to see that happen more regularly. To support

collaborative efforts across states, to develop guidelines and standards based on science, and I'm very, very pleased with the U.S. Department of Education's efforts to promote that. And to consider the funding needs of state service delivery systems relative to providing high quality care for children with autism and their families. Thank you.

Mr. Grossman: I want to thank all the presenters for surviving the technical difficulties we were all having. [Laughter.]

Mr. Grossman: In the next 15 minutes or so that we have allotted to us, I'm going to first open this up to the panel and then open it up to everybody to ask us questions. But the one question I have and what we saw as our role in presenting this panel was for these individuals here to present to the Committee what they thought as kind of the take-home message of what they believe is necessary for this Committee to respond to this powder keg that we're sitting on in terms of the service sector. So we'll start with I guess Donna.

Dr. Noyes: Do you want me to repeat the recommendations?

Mr. Grossman: What would be your main take-home point for this Committee, for the IADD Committee, in dealing with the service aspects of autism?

Dr. Noyes: I think my main take-home point would really be that we are at the state level increasingly under a lot of pressure to have evidence behind our work and to show that interventions can be effective. And I'm very pleased with the level of research that's going on. I think it would be important, though, to also think about how we can do more research that would interface with the service delivery systems for children with autism and possibly how we can make use of some of the data that states are collecting or have improved collaborative efforts among research teams and states to address some of the service delivery and practice issues related to children with autism and their families.

Dr. Holmes: I think for adults with autism, we have to look at the issue of entitlement which

would bring funding and support. We have to look at the adult population as learners still. So I think we just have to look at how are we going to bridge that from 21 when there's so much laws and regulations to provide appropriate education, what can happen after 21. And the other main goal that I would like you all to take home is that dilemma of how can we create career paths for those individuals that work with the adult population, and how can we approach that from the higher education standpoint.

Dr. Pratt: I think that all of us sitting here on this panel and probably several of you too feel this kind of ominous black hole that we're in. And I think that we're always overwhelmed by all the work there is to do, and I'm sure that families feel themselves in that black hole. So trying to think about in 30 seconds what's really needed, I think more of this and more funding. I'm happy to see that Thomas Scully from Medicare and Medicaid is on. I hope that we would get people involved with the insurance industry. I hope you would get people involved with juvenile justice system and

the criminal justice system. I would hope that education would partner with the mental health community to look at the complexity of these individuals' needs, and I hope that we would also access the resources that we currently have. We have a lot of energy. We have several family members here and several family members who are a part of this Committee to really kind of coordinate ourselves and coordinate our momentum to try to start digging us out of this very large black hole. I get phone calls every day, and I personally wish that I could write checks. But since I also have a government job, it just isn't possible to be able to do that. They'd be very small checks. But it is overwhelming. And I think one of the things, though, that I do want to say is, this is a ray of light, this Committee, for families and for us professionals who are out there getting those phone calls every day. So thank you for being here all day.

Ms. Alfreds: I have more than one point. One is that there is tremendous energy in the family movements, and it would be wonderful if they could

come together across disciplines. Again, these families tend to walk in a lot of different doors, particularly if their needs are complicated, which is what the public system sees. And there are so many gray areas, with all due respect to research and categories, but many of these kids and families through long histories of closed doors don't neatly fit anywhere. And really it's within our communities that we're trying to bring the best research, the best approaches, the best interventions. But it's complicated. It's individualized. And the more of us that are at the table together working on it, the better. One point that I didn't make: There is disturbing increases in medication of very young children in the mental health system. I think we all know that. We've seen the articles. And I think we need the research minds looking at what the implications are for children who are coming in, again, often the mental health door, because they are landing in psychiatric facilities and psychiatric systems.

Mr. Grossman: Barry?

Dr. Gordon: One of the reasons people use to deny services is there's no agreement on what services should be provided. And this is kind of a question for Anne and Donna but really for the entire panel. Do you actually think -- let's take in one area, say, education, that you disagree or agree with the New York report, the National Academy of Sciences report, the Eden model -- are they fundamentally in disagreement or are they fundamentally in agreement on what ideally should be done for children?

Dr. Holmes: I think they're generally in agreement. I think we're past that now. I think there's some subtle differences, but I think that the general strategies, behavioral strategies that are being used, they aren't being argued as they were ten years ago, 15 years ago. I find lack of people wanting to provide the services and in the public system that we deal with or that through Eden we deal with, is it's tough. And they sort of know that that's what they have to do, but it's really tough to do it, and it takes a lot of money, and it takes the training and it takes all

those pieces. But I don't see a lot of fighting about approaches anymore.

Dr. Noyes: I would generally agree. I would also just add that when we issued our guidelines in New York -- and they are science-based guidelines, looked at evidence and the panel made recommendations based on the evidence -- we had a series of dissemination and training sessions and we had some very strong supporters and some people who were very, very upset at the recommendations and the guidelines. So I agree that there probably is increasing agreement, but I do think that there probably still are some issues around approach and intensity that will continue to be discussed.

Mr. Grossman: One of the things addressing this question also is that these people here represent programs that are working. The reality is, is that 90 percent of the programs out there or what are called programs aren't working. And your question is a great question, because I think there is a consolidation of thought of what programs -- what is needed in the therapies for these children. In most places, those services are

denied. They're just not available for whatever reason, funding reasons, philosophical reasons, in many ways, and it's something that we tried to address a couple of months ago with the Psychosocial and Behavioral Interventions Workshop is that some of the service delivery programs will deny services because there's no scientific evidence behind discrete trial training, ABA, et cetera. So that's the problem that the vast majority are dealing with.

Dr. Insel: We need to wrap this up in a couple of minutes, but let's get some more comments.

Dr. Zeph: I think that we're in the same situation here that we started this morning in terms of the screening instruments. And what we said was, we have some adequate place to begin. I'll tell you, if there was a service out there that was doing it, that was having the kind of outcome that we all dream of, we'd all know about it and there wouldn't be this discussion. The fact is, we need more research that looks at the wide range of possibilities. I don't think we know what's possible. And as long as we put any kind of

blinders on ourselves, we're not going to know what's possible. We need to really tie together the research and the practice. We need to look at it. We need to remain open to all possibilities. We are our own worst enemies at that sometimes. And we really need to look at what or listen to what families are telling us in terms of what's possible. I know one thing as a diagnostician and as an evaluator that we don't find what we don't go looking for. And one of the questions that I use with families that I learned along the way is tell me about your child and tell me one thing that your child has done that you never dreamed they would be able to do and something that you might not even have told anyone about because you thought that they would think you were crazy. And I get the most incredible stories from families. Parents will break down in tears because of things that have happened and the reactions, if they've tried to tell this story to many professionals, which is you're being unrealistic, you're in denial, those things can't possibly be true. So there are little miracles that happen out there,

and what we need to do is really be open to them and really use them as the basis for opening our eyes and our minds. The combination of research and practice is probably the greatest area, from my perspective, that we need to deal with.

Dr. Insel: I think in view of the time, we're going to have stop in two minutes. If we could have just brief comments.

Dr. Cordero: Just a brief comment. I think that everyone would agree that there are more and more cases of autism that are being reported and that also they are aging. And one of the issues and I think another group that we need to look at that actually could be an important group is all the group of individuals with mental retardation or cognitive deficiencies. The Surgeon General's Report on Mental Retardation. If you look at the issues of access, and many of the issues that are in that report, I think echo what was described here. And really it is about the transition between childhood to adulthood. We have probably not a perfect but some sort of a safety net for children up to about 18. But in fact what we're

missing is almost like health care for individuals with special health care needs and special health care services in 18 and older. And I think that it is a generic issue, it is familiar issue for individuals with autism, but we need to look at it as sort of a national issue that needs to be on the national agenda.

Ms. Goldman: You began this session, Dr. Insel, with asking what was the role of the Committee. And I think that's something we are struggling with. When we put together this panel, it was to begin to show the complexity of these issues, that it involves multiple systems, multiple funding streams, multiple levels, from national, state and local across the age span, services, workforce, all of those things. And so one of our challenges as a Committee is to figure out how do we get a handle on this through this Interagency Autism Coordinating Committee. Right now on this Committee we have HRSA representatives, SAMSA, Lucille and Lee, from their perspectives and Anne from NIMH. But we do need other I think systems, federal agencies

involved. And I think we do need to either get some direction from the larger committee or really figure out how we get our hands around the broad scope that's implied with what you heard here, which is really just the tip of the iceberg. Dr. Insel: If we can end this session, I think that's a good place to try to sum it. And maybe, Rick, you can hear your comments later, because I'd like to. I think it's going to be critical to know what are the next steps and to come away with a process here that will be enriching and will take us one step further. I must say in listening to the presentations though I agree the challenge seems overwhelming and there is tremendous fragmentation and some horrendous situations, there's also a lot of hope in terms of some things that are happening in a diffuse way and some things that really do seem to make a difference. And it's a question of how to optimize those and bring them together. From what I'm hearing, I don't think the subcommittee is actually quite large enough. I mean, there are some other parties that need to be at this table. We haven't heard the Medicare

perspective, for instance, which would be an important piece. And that's something that can be developed. It would be helpful for us I think for you to, as we said for the Steering Committee, to come together with some kind of a written document. It doesn't have to be long, but it does need to have some action items that we can then all talk about. I don't think we have to wait six months to respond. These are things that we can begin to deal with electronically. Also, I'd really like to thank all of the presenters and ask if we could have your Powerpoint presentations again as something we could include on the Web site so people can refer back to them. It's an outstanding set of presentations and a very good discussion. I just wish we had more time. But I think in the interest of everyone here and the other presenters that are coming up, I'd like to take a break now for about 15 minutes -- let's say 10 minutes. Let's reconvene at 3:25. Thank you.

[Recess.]

Dr. Insel: Let's get started here. [Pause.] We have Redskins tickets for anybody sitting down. [Laughter.]

Dr. Insel: All right. We're running a little bit behind schedule, so I want to launch into the next session. There will be a few people who are having to separate from their cookies, but they will do that momentarily. The next presentation is a focus on the Pharmacotherapy in Autism Results. We're going to first talk about a sort of general Psychopharmacology in Autism, and Kathryn Carbone from the FDA will begin that presentation. Dr. Carbone, I'd suggest we wait about ten seconds until we see a few more people come through the door, and then we'll launch. [Slide.]

Dr. Carbone: I've been accused of talking too fast, so maybe that's a good thing this late in the afternoon. [Slide.] These slides will be up and available, I've been told, so I'm going to hit the highlights for time awareness here. Special issues in autism for treatment, of course, as I mentioned it had severe persistent symptoms. Symptomatic therapy is likely to be lifelong,

which raises significant issues in therapy. Side effects become a concern and adverse events when you are talking about treating people for upwards of 80 years. In addition, we have to have treatments that are safe for children as well as adults, and children are a special population that's under considerable focus right now at the FDA. However, the good news is, is that this is a disease which is clearly recognized to have a biological basis, and that if we knew what the basis was, we could significantly impact the course through prevention. As a developmental disease, intervention is by nature a possibility. However, it would be time critical. Throughout the talk I'm sort of going to go with the "what if". Because as was mentioned, if we don't keep the "what if" in mind, we sort of stagnate. So what if? What if prevention of a neurological disease, something early during birth, for example, or during gestation, fully therapy. Okay. Symptomatic treatment. Significant quality of life improvements. We could never overlook this. The last session emphasized that it's absolutely

critical. And its successful treatment of several of the core symptoms of autism could significantly improve the life of many people in the United States and elsewhere. However, we have to remember that symptomatic treatment may fail to address mechanism, it may fail to address cure. So in the what if portion of this slide, we must always keep those in mind. [Slide.] Quandaries in symptomatic treatment approach is that in autism specifically, there have been many promising therapies that have been suggested but no treatment when carefully studied in a critical way, and we'll talk about that, has really been as good as initially hoped. We'll talk about specific treatment at the end of the second talk in this section. But in general, that's true. In a behaviorally -- a disease, which is the good news, can be affected significantly by behavioral therapy. The bad news is that this often makes it difficult to study other kinds of therapy because of placebo effect. I'm going to go very briefly over how we make decisions about data and quality of studies when reviewing the issue, is a particular treatment safe and effective for a

particular disease or syndrome. And so data for treatment decisions can come in from case reports, case series and prospective studies, clinical trials, open cohort and double-blind randomized. And those are sort of listed in order of quality of the data. In other words, reproducibility and objectivity of the data. Just briefly, case reports. The good news is that many interesting therapies are identified initially by cases. The first fellow who thought to brew up willow tree bark for his headache was very perceptive, because that contains aspirin, essentially aspirin compound. However, the problem is, is what you get reported are obviously only the successes. So that case report is going to report a success, and then the linkage of actual causality of success needs to be determined. Case series are a little better in that you have a series of patients who appear to have responded to a particular therapy. The evidence strength of those data go up a little bit, but the problem is once again, one reports the successful cases. One reports what are usually retrospective analyses, and there's no consistency

of an analysis of the data. A prospective study has improved the quality of data because it's preplanned study. There's a routine measure of the outcome so that it makes comparability among groups easier. And in an open trial, which is often the first step in a new medical therapy, is that both the patients, the treated and the researchers, know the therapy that's given. And there's an inherent tendency towards a bias. It's not an accusation of deliberate misintent, but it simply happens. There have been studies that even show if a particular study may be funded from a particular source that there tends to be a bias that may enter. So being an open label study, difficulties can arise. However, in an open label study, there are issues of discontinuation. You treat, measure, stop treatment, look at the loss of effect, or treat, switch to another treatment and compare the two effects. There are ways of getting a little more comparable data. However, it's very important in using psychotropic medications to be aware of the washout. In other words, the discontinuation must be measured after

it's clear that the drug therapy has left the body at significant levels. Cohort study is a little bit of an improvement. Two groups. Typically one treated and untreated are followed prospectively. They can be open or blinded. We'll talk about blinded soon. However, as has already been mentioned at this meeting, whenever you get a placebo trial, a trial that involves a placebo, there's some reluctance to enter therapy. In a case where there is an effective therapy, many times a placebo trial is considered not ethical and a comparison of two therapies is used. [Slide.] And probably the best quality data comes from a double blind, meaning the patient and the practitioner are both blinded as to the particular treatment, randomized so that the group of patients are not selected but they are randomly sent to each group, and they're controlled usually with either another medication or a placebo. However, it's been noted that the specific comparator to the experimental medication should be a well -- it's best if it's a well-established, well-documented therapy. But of course there

aren't any really in autism at this juncture. And you can both look for equivalents between two therapies or probably a superior way of looking at superiority of one drug over another. And you can continue to use other designs. [Slide.] Special considerations in autism spectrum disorders is consent, because the individual even as an adult may not be competent to give consent, so they require a person to give consent. And then of course whenever you're doing a trial where the individual receiving the therapy is not the person giving consent, there are issues of risk. Perhaps a smaller risk is accepted when the person is not capable of giving informed consent themselves. Disabling behavioral symptoms and placebo use or placebo effect can affect being able to measure the outcome of the study. The language problems that have been mentioned earlier may affect the ability to provide feedback about internal state. In other words, is the child now less hyperactive because they're simply sedated, or do they actually feel less anxious? If they're not able to communicate, that's hard to determine. And of

course, the disorder is quite heterogeneous, so that the selection of particular subgroups and responses by particular subgroups based on differences in a biology that we don't understand are important considerations. So, as was mentioned in an earlier talk, I think that going to the direction of finding the correct subsets to test may be very important. [Slide.] What does the FDA do? Well, FDA has the ultimate responsibility for determining whether a drug or biologic or device is efficacious and safe for treatment of a specific disorder. There are many other features of the FDA, including potency determinations and purity determinations and inspection, et cetera. But basically, is this decision is this drug based on a risk/benefit analysis, is the drug effective enough and safe enough to be recommended for use for a particular disorder? I just want to make it clear that when we evaluate the data, be it animal toxicity data all the way up to clinical studies, we evaluate very carefully the design issues. There have been times -- what you see published and what actually is part of the review are

sometimes two different things. There have been times when specific studies may be cited and published, but they're not used for efficacy analysis because a flaw has been determined in the study and therefore the data aren't felt to be acceptable. All studies are basically reviewed for safety. Regardless of study design, safety is an issue. But for efficacy, if the study design is lacking, the data will not be used for efficacy. One example, I won't mention the product, but one example was a change in the clinical outcome in the midstream of the study. In other words, the clinical end point was determined to be X. The investigator said we want to change it to Y in the middle of a blinded study, and we said you can't do that, suddenly change an end point in a study and then consider it a blinded study, and therefore we won't use the data. And they changed it anyway. We don't control that. The FDA, in terms of reviewing for drugs, the FDA is an organization which takes in the information, the applications from the sponsors, and we review what is presented to us. There also is an arm in the

Center for Biologics, this is particularly true, which is here on the NIH campus, a research end, and efforts would also include in our particular area is we do research on animal models of neurovirulence, of virus neurovirulence, and actually have an animal model of autism. So there are research components where we try and contribute as well. When reviewing clinical studies, superior outcomes are preferred over equivalence trials, because small margins are difficult to prove statistically. If you have a big difference, then statistically that's easy to feel comfortable with accuracy. In addition, there tends to be, as with an IOM report, a summary of a consistent body of evidence that continues to support the use of the drug. In other words, evidence where you have yes/no, yes/no, yes/no in a series of trials suggests the ability to show that this drug is effective is limited. Several well designed trials that say yes, yes, yes, yes, yes, then confidence increases that the drug is going to be effective. However, you may or may not know that any drug that's once approved by the FDA

can be used by a physician in an off-label use, and I'm sure many of you are aware of that. In other words, it's used for a disease that has not specifically been -- it has not been studied for that disease. If you want to find out specifically about off-label use, literally read the drug label. Because the drug label will say this drug is approved for, and these are the studies as to why it was approved for that. So that's one helpful bit of information. [Slide.] I'm not going to go through these in detail other than to say in these sorts of issues where these are difficult and complicated syndromes, the ability to define the quality of evidence that must reach a certain threshold for approval has been fairly well discussed by many different groups. And how it basically works is that list that I went from sort of the least quantifiable data to the most objective quantifiable data, if you reverse that list and go from top to bottom, those are the kind of studies that lend the most credence for approval of a drug. [Slide.] In addition, as I was saying, the preponderance of evidence is often the

final positive step in approval of a drug in that if a meta-analysis of many, many studies comes up with a clear indication that the drug is efficacious and safe, the safety review is adequate, then that is probably the highest evidence for support of a drug. But there are others, and I'll leave the Web site for the details. [Slide.] I think clinical studies for autism treatments, the problems that are run into many times is clear specification of the sample being studied is a major limitation. Biological markers are wonderful. If you took a group of people with immunodeficiency and treated them all with AZT, some would respond, because some of those people will have HIV. But if you can't separate out the segment of people that are immunodeficient because they have HIV, you may completely wash out the effect within the larger group of people with immunodeficiencies, is an example. So being able to define subgroups or having a clear biological marker would be a tremendous boon to clinical study design. Clear specification of the treatment is very important.

Random assignment is critical. And metal analyses are unlikely to be helpful in the case of autism. I said in general they're helpful. In the case of autism data, they're not currently that helpful because -- with the exception of perhaps some very recent studies, several of which will be discussed after me -- there really are small numbers of controlled studies with small sample sizes, nonstandardized outcomes, people using a variety of tests. And I would like to emphasize the importance in the setting of a developmental disease that may occur very, very early, the ability to segregate subsets of children by even pre-verbal, very early infancy types of tests, one of which was sort of suggested in preliminary data with the eye attention test and the lights. The ability to, in the case of, for example, safety analyses, which are very important to the FDA, and continuing safety evaluation of even licensed products, you could imagine the benefit of being able to clearly categorize infants very young before and after vaccination to answer public concerns, for example. At this point, there are

very few therapies that you can say are unequivocally of major benefit for the treatment of autism in terms of symptoms. There is virtually nothing really in terms of prevention or cure. These are categories that people have come up with as ways of sort of categorizing data and treatments. Some may be unsupported but are potentially useful, possibly efficacious; [Slide.] Probably efficacious; [Slide.] And a well-established treatment. And the criteria for well-established are fairly strict. [Slide.] So I'm just going to briefly finish up by running through a group of studies or group of drug categories that have been tested in autism. Time doesn't permit a detailed discussion of one of the more interesting ones that will be discussed in detail following this talk, but in general, traditional antipsychotics have been used in treatment of children with autism or autism spectrum disorder. They probably fall into the probably efficacious. There have been improvements in hyperactivity aggression, social issues, learning, stereotypy, et cetera. Side effects include sedation. There

are other side effects which may be permanent with these medications. Forty percent of the children with sudden withdrawal may have movement disorders that's increased in girls and increased after long therapy, and long therapy of course being an issue in autism. And I think it's very interesting to look at that setting and ask the question, why would little girls be more susceptible to these side effects than little boys? [Slide.] There are atypical antipsychotics. These are newer drugs that have different mechanisms of action, or at least different chemical bases. They appear to have fewer movement side effects. They have better reduction of negative symptoms. A negative symptom is sort of a persistent social, absence of normal social behavior that occurs in schizophrenia in between episodes of acute psychosis, and they're somewhat reminiscent of the withdrawal and negative symptoms seen with autism. These fall again into the category of probably efficacious, but it's variable. It depends a great deal on which of the atypical antipsychotics are used, and have many of the same positive benefits, or have

reported the same positive benefits as the traditional antipsychotics. Sedation. Weight gain can be quite significant, cardiac changes and seizures. So of course when you talk about whether drugs are approvable for a license or for a particular treatment of a particular condition, there's risk and benefit and serious side effects in the lifelong therapy are of great concern. [Slide.] The serotonin reuptake inhibitors. Serotonin has been one of the neurotransmitter abnormalities that has been -- consistently seems to be popping up in many different studies of children with autism, both imaging studies in the brain as well as serological studies of neurotransmitters. And many of the behaviors that appear in autism are somewhat reminiscent of obsessive-compulsive disorder, for example, is treated with this classification of drugs. There is some -- and I'm generalizing here. You'll probably find exceptions to everything say. But in general, there is some feeling that older individuals with autism benefit from these drugs for improvement of repetitive thoughts and

behaviors, aggression, language. Children, the data are somewhat more conflicting whether they work. And there are variable side effects depending on each of the drugs. And I guess the finding that there are age-specific differences in outcomes should not be surprising in a developmental-type disease. [Slide.] Secretin has been mentioned. It's a peptide hormone. It does these various things. It was cited originally in a case report but has really, really failed to show efficacy in placebo-controlled studies and blind studies. It, however, is felt to have minimal side effects, but the question is if multiple injections of a foreign protein may result in an allergy which could be serious. [Slide.] Vitamin B6 is utilized in the synthesis of several neurotransmitters. Selective studies using selected individuals showed some positive results. Standard rating scales generally weren't used. There was at least one small double-blind placebo-controlled crossover study that failed to identify benefit, and the feeling is minimal side effects, potential benefit in this treatment. [Slide.]

Naltrexone blocks the effects of opiates. Opiates are essential natural morphine derivatives, and believed to be released during androgenous, self-injurious, repetitive behaviors. The assessment may be possibly to probably efficacious in reducing hyperactivity and impulsivity, but there's some question of long-term benefit. Some studies actually showed worsening. It may be a function of the patient's age, and a side effect in this case, if it's material, it's very bitter. It's administered orally. [Slide.] Methylphenidate is used to treat ADHD, attention deficit hyperactivity disorder, and may have modest results. Statistically significant effect on hyperactivity. However, in a double-blind, placebo-controlled crossover study, just recently been reported, the response of methylphenidate in ADHD may be associated with increased phenylethylamine levels in urine. And what that means is that the children who responded showed this compound in the urine, and the children who did not respond -- this is with ADHD -- did not show it. Now that's one small study. It needs to

be repeated, et cetera. But these are the kinds of biological tests that may be very helpful in, again, subgroup type identification. Children can be given a test dose. If they metabolize the material and it's found in their urine, then maybe they'll be classified as a potential responder and more likely to benefit from the drug. But that's all in theory. Larger trials may seem warranted for certain indications for this drug. [Slide.] Anticonvulsants. One of them is a novel anticonvulsant with an unknown mechanism. It's a cognitive enhancer. There was an open label very small study and showed some interesting positive outcome, but again, requiring additional study to come to any conclusion. [Slide.] Immunoglobulin has been popular. There was some benefit in some small open label studies. There have been mixed response even within those studies. There appeared to be children who claimed to have clearly benefitted, children who did not. Clearly, more research is needed if this is going to be pursued as a therapy, because the question of the mechanism. And keep in mind that it's traumatic.

It requires IV treatment, transfusion of a human blood product, which is not an insignificant risk for an unsupported therapy. And then there are supply issues with obtaining this material, even for indicated and proven outcomes. [Slide.] Tetrahydrobiopterin has been used. It's a co-factor for tyrozine and hydroxylase in the biosynthetic pathway of neurotransmitters. It's used to boost the levels of serotonin in dopamine. An open label study that looked promising. A few side effects reported. But again, as you can see from the earlier discussion, this is a very preliminary type study. [Slide.] So limitations in autism clinical studies. And this is a big issue for the FDA, because remember, we review the toto of the work, the research. It's not study-by-study, but the body of the work that is our interest, although obviously we interface with each study as it becomes an IND. When we talk about review for licensing, it becomes the body of data, both safety and efficacy. And pattern of encouraging case reports in autism has typically been followed by unsubstantiated or modest

outcomes in much more rigorous studies. Even good studies tend to have very limited sample sizes. To remind you, this is public information that's been announced by the sponsor, so I can say it, we are currently undergoing a study involving 100,000 children for a trial of vaccine. We do that in part so we can pick up very rare adverse events and so that we can see efficacy. And contrast that to a study in autism which might have 250 children to try and make a determination. There tends to be, when there is a positive outcome, it's not in every subject. Obviously we discussed the heterogeneity of the disease, the placebo responses. Rating scales may not be specific to autism. Short-term studies for chronic disease. I think this should be highlighted as a real significant issue in autism. And then symptomatic versus curative or preventative. It's not an either/or. It's just that both sides of the coin need to be addressed. [Slide.] Treatment implications. To summarize, there's no evidence currently about any drug, although in the more recent data we will see that pharmacological

treatment dramatically changes the core symptoms or course of autism. However, we would hope that at some point to identify very early therapies with specific agents that may be preventative and eventually identify the subjects, the specific subjects that may be helped by each particular intervention. And we clearly need better work as well that the pharmacological treatments to improve function. That's probably where most of the strides have been made, but they're still modest. And it's difficult to associate a particular therapy with improvement of specific symptoms, and age dependence is a feature of efficacy. [Slide.] Future research directions. This is my big "what if" slide. Discerning mechanisms. Timing of the neurological basis for symptoms would permit direct treatment, and which is "what if". It tends to be for psychiatric diseases which for the most part are symptomatic treatments. This is a big what if to actually find a mechanism for this disease and treat that itself. Defining specific subgroups. I can't emphasize more from a point of view of review of

these studies and the data that having a biological marker for subsets would be phenomenally valuable. And that, as has been said before, the treatment should become as evidence-based as possible. Exposure to unsubstantiated treatments may have adverse effects, or even if they don't, reduce access to more efficacious treatments. Think laetrile. The big crime with laetrile was -- it had some bad side effects, but the big crime was if someone went in and had laetrile treatments instead of a proven therapy, that was the major disappointment there. [Slide.] So I'll just leave this slide up to let you read through it. This is what keeps me going in our darkest hours of granting and publishing and presenting at meetings. [Laughter.]

Dr. Carbone: But the message really -- and I left the one off about peer reviewed, because I didn't want to upset anybody here. But the message is encourage originality in research. True originality should be encouraged, but never, never, never neglect the quality and proof, because that's where the money is. Thank you.

Dr. Insel: Thank you, Kathy. Two points of clarification just so that we're all on the same page. Is any compound currently indicated by the FDA, or approved by the FDA for its use in autism? Point one. And point two is, is there any effort currently in light of your last point, to develop compounds that are specific for autism rather than just using compounds that are currently used for something else and trying to apply them off label to autism?

Dr. Carbone: I think what I'll do is, because -- on the second point, we're not really at liberty to discuss anything that hasn't been publicly released by the sponsor. And from a literature search, I couldn't identify anything I could really let you know about. So I have to defer that one, because I can only release information that's been public knowledge. The first question you asked, I will also have to defer that to my colleagues at CDR, because that's very complicated. I don't want to say no only to find out that one small list somewhere has been attempted for autism. So I'll be happy to get a

list that's very accurate and up to date. I don't want to do this off the top of my head. Sometimes it's buried in a label somewhere, and I don't want to be misleading.

Mr. Shestack: If you're asking if there's any concerted effort that we don't know about in pharmaceuticals to actively look for compounds for autism, I think the answer would be no, there is no concerted effort that any of us in the voluntary groups know or who fund research know about. There may be things that have off-label indications. And in the future as we look for like public-private partnership, if there ways for the federal government to encourage pharmaceutical investment in autism, given the numbers we have right now, and the lifelong condition. I mean, we spend a lot of time trying to convince people the obvious, which is that they could make some money if they served this market. And it would be good if they would hear it from you guys.

Dr. Insel: Just to underline that point, we've been listening all day to rather scary predictions of what the prevalence of this disorder will look

like in ten years. Big pharm is very heavily invested in creating yet another antipsychotic or another antidepressant, which is a market in both cases, both markets are relatively saturated. If what you're telling us is that there are no compounds currently that really show great promise here, one might ask why no one is really putting the best minds at big pharma into looking for this as a unique and new application for which actually there'd be no competition currently.

Mr. Shestack: Wait a second. One of the reasons is typically, among others, big pharma waits for academic -- for a big hit out of academia, whether it's going to come from neuroscience, from the imaging stuff we were talking about, or whether someone's going to find a couple of genes, that's what they wait for. And so honestly, I know you hate when somebody says like throwing money at a problem doesn't solve it, but actually a little bit more resources to get the first big biological hits is probably the most direct thing that the NIH could do to get pharma

to invest. I know that's not what any of us really want to hear.

Dr. Vitiello: Yes, but, John, we kept genes for rats syndrome. And I think it's extraordinarily difficult, and of course there isn't a lot of interest in private industry to develop genetic therapy for Fragile X.

Mr. Shestack: The point is, it's finding a pathway. And the other thing is, it's not a competitive sport. But there's what we now know is there is a much bigger market. There are a lot of people who have autism. So it still has to be encouraged.

Dr. Carbone: My sort of ignorant bias, being a neurovirologist backed into autism is that I think part of the problem is the lack of a good biological model in neuropsychiatric diseases in general. I had a discussion with someone very prominent in schizophrenia who said we don't need an animal model. I have 100 schizophrenic brains in my collection. And I said, when does schizophrenia develop? She said, I don't know. I said, what's the mechanism of damage? I don't

know. How do the drugs work? I don't know. What's the average age of the brain? Thirty-one. But you can't tell me if it develops -- is it a developmental disease in utero? I said, you know, I think you do need an animal model. And I think that drugs are the same thing. We actually have explored our model of disease virus using several different drugs and have found two things. One, that some are effective in the species- specific behaviors we measure. The second thing is we found genetic background effects. We have a couple of publications on that, that it used two different drugs in two rats with the same infection at the same time, that we have different outcomes because they come from two different strains of rats, and we're currently working on that. So I think it would be interesting if we could at least begin to look at some possible interventions based on some animal model systems, because that way you can explore a large number of drugs fairly cheaply. Clinical trials are very expensive, and obviously there are ethical issues.

Dr. Insel: Let's move along here. And the next presentation will be from Ben Vitiello focusing one specific finding recently around the atypical antipsychotic risperidone. Ben, your particular Powerpoint presentation here is not what any of us would have expected. [Laughter.]

Dr. Insel: If only we could hear it as well as we could see it. [Laughter.]

Dr. Vitiello: I am Ben Vitiello. I am with the Child Treatment Branch at NMIH, so what we do we basically are clinical trials to try to test the effects of treatment in kids. And research in autism is part of our program. I am going to report briefly on a study on the use of risperidone in children with autism and serious behavioral problems. Most of what I'm going to say has already been published in the New England Journal of Medicine in August. You might have already seen the paper. If not, if you are interested, I have copies there. You can just take a copy. The idea here is not basically to cure autism, because we don't think that risperidone unfortunately kept that promise. The study was

launched in order to see if risperidone could be helpful to alleviate the serious behavioral problems such as self-injury, aggression, agitation, severe compulsive behavior that impair the life quality of children with autism. As has already been presented by the previous speaker, agents that are called antipsychotics, meaning that are used to treat psychosis, have traditionally been used to control also behaviors such as self-injury, agitation, aggression in patients. And they have side effects and they are being replaced in the last ten years by the so-called atypical, which is a second generation of medication that is better tolerated not only, but it seems also to have efficacy on the so-called negative symptoms of schizophrenia. There are no good symptoms of schizophrenia, but basically the symptoms are divided into positive, which means hallucinations, delusions, and negative, which means social withdrawal, poverty of thinking, for instance, cognitive impairment. And it looks like the atypical are good also for the so- called negative symptoms. So it's very relevant to study

atypical in autism, because there is also some hope that it may also improve the ability to interact socially and to think more clearly for these patients in this condition. [Slide.] Now the study was conducted by the Research Unit on Pediatric Psychopharmacology, which is a network funded by NMIH through contracts that was established in '97, with the purpose to test medications that act on the brain that are commonly used in our communities off label without having data, good data to support the efficacy and safety. Dr. Carbone has pointed out that once the drug is approved, it goes into the community, clinicians start using it for indications that are not what was originally approved. So the purpose of RUPP, as we call it, was to try to fill the gaps for those conditions that were more important for kids. So there was a particular group of RUPPs that identified risperidone as being something of public health importance because it was commonly used to manage severe behavioral symptoms in the context of autism, is used off label. There was little interest from industry in this type of

research, and there were not enough data to support its efficacy or safety. [Slide.] This particular group of RUPPs included researchers at different universities, including also researchers at NIMH. It was monitored by the Data and Safety Monitoring Board of NIMH that review the data periodically every three months. [Slide.] Basically, the study enrolled subjects: children aged 5 to 17, with autistic disorder. So this is not autism spectrum disorder. It's just autistic disorder and severe behavioral problems such as self-injury, aggression or agitation: One hundred patients. Patients were randomized, and they were randomly assigned to receive either risperidone or a placebo for eight weeks. The main hypothesis was risperidone would be superior to placebo in improving the behavior by alleviating impulsive, aggression, agitation and self-injurious behavior. [Slide.] The design basically was a double-blind placebo controlled study, an eight-week double-blind control phase, followed by another period of four months for those patients who have improved. Basically it was double blind, and then there was

an open-label trial for those children who were assigned to placebo, and they didn't improve, just to be fair to everyone. So if you were randomized to placebo and you wouldn't improve on placebo, you were offered at random study eight weeks of risperidone in open label. And if you are a responder, you enter into a four-month, open-label extension, at the end of which there was a double-blind placebo substitution so that patients were randomly assigned either to receive placebo and continue risperidone. And the purpose of this was to see if you still needed to continue taking risperidone after having improved for six months. [Slide.] I'm skipping forward. The dose basically varied according to the weight of the child. So the study dose was 0.25 for very young kids with a weight below 20 kilos, was 0.5 for kids who are older, and the maximum dose, it was titrated based on efficacy, on clinical response and presence of side effects. The maximum dose was 2.5 for the younger children and 3.5 for older children a day on a BID, meaning twice a day schedule. [Slide.] It just shows the variables of the sample, and the

randomization actually did its purpose, meaning that all these variables were basically balanced very nicely like age, sex, ratio, ethnicity, tanner stage were quite comparable in the two groups, risperidone and placebo, which is what you want in a randomized clinical trial. [Slide.] And also the psychopathology as measured with this ABC scale that was developed really for kids with developmental disabilities was sort of comparable in the two treatment arms. That's really what we want. [Slide.] And other variables like family income, living situation, IQ were also comparable in the two groups. By the way, most of these children suffered from mild to moderate mental retardation in addition to autism. Only about 5 percent had normal IQ. [Slide.] This slide shows you the main result at eight weeks. This is the severity of the symptoms. If the symptoms go down, it's good. This is the actual curve with all the points. The straight line is the random regression line, so it would give you the average basically for the group. So the red is placebo. You see there is some decline, but not that much. And this

is the risperidone. So there is quite a huge difference between the two treatment arms that is highly statistically significant and also highly clinically significant. [Slide.] And if you want to plot the number of patients who are called the responders at the end of eight weeks, you see that about 80 percent in the risperidone were responders and less than 20 percent of the placebo were responders. [Slide.] Now clinical trials, unfortunately, present the data in a sort of a group mean, in a sort of probabilistic way, so it doesn't tell you too much. It doesn't give you a sense of how much the drug actually helped the individual patient. So what we are also doing now is doing another analysis of outcome data using the so-called target symptoms, which is an innovative system that we introduced for this study where basically if a child met all the inclusion criteria for the protocol, the parent was asked to identify the two major behaviors that were really of concern to the parent, and the improvement of these target symptoms was monitored throughout the study. So then we are able to see

what is the impact of the treatment not only on the average symptoms of a child but on those very top concerns and complaints, you will say a chief complaint if you're a clinician, that brought the patient into the protocol. This is a paper in preparation that we need to submit. But to give you just an example, just a flavor of the type of problem. So at baseline, tantrums twice a day lasting 10 to 15 minutes each. Throwing self on the floor, flailing arms, breaking furniture, hurting other child if in the way. Incidental damage to self. Parents won't take out in public. At random study for this particular patient who was a responder, tantrum twice in past week. So tantrum still present, but not every day now. Twice in the past week, lasting about five minutes each. Stomping and screaming without damage or injury. Stays off of floor. Parents now willing to take out. Just an example, so that it does make a difference. It does make a difference, improves also social withdrawal, improves stereotypies, improves hyperactivity and also inappropriate speech, very little. This is an effect side. The

larger this number, the greater is the difference of the risperidone versus the placebo. So on hyperactivity is a big effect we say. On inappropriate speech is a small effect. [Slide.] However, the improvement has also several drawbacks. And one of the major drawbacks is that there is a significant weight gain. On average, these children gain almost 3 kilos, which would be six pounds, in the eight weeks, in two months of treatment. With the placebo, only one. There was also fatigue. There was drowsiness and there was tremor. The good news is that the so-called neurological extrapyramidal side effects were fairly mild, besides tremor. But kids didn't have dystonias, which are abnormal movements that sometime affect the neck, mainly the neck or the face or sometimes a finger. So that was the good news. But still there were side effects that were sort of worrisome. [Slide.] When the children were switched after improvement to placebo, there was a high incidence of relapse, you know, 62 percent relapsed. Interesting that 12 percent relapsed even if they stayed on risperidone. I call this

the nocebo effect, meeting the expectation of worsening. When you do a placebo control and you want to improve, you introduce a drug, there's an expectation of improvement, you've got a placebo. When you discontinue the drug there is an expectation of worsening, so everyone gets worse and starts reporting symptoms. And so this is the nocebo effect, which is interesting for us in the clinical trials. What is interesting is that there is about one-third at least of children who do not relapse. And so it will be interesting to know which ones are the ones that don't require long-term treatment with risperidone. Unfortunately, the study has a small sample size, a small sample size because the DSMB stopped the study because we had reached a significant result, and they didn't think it was ethical for us to continue randomized patient into placebo, and so they told us stop the study because you have reached a conclusion on the primary hypothesis, and the subgroup analyses are not the primary purpose of the study. So, unfortunately, we cannot comment on which subgroup of patients may be more likely to stay well

without the risperidone after having improved for several months. [Slide.] I think I need to stop. But the conclusion basically is risperidone works, it does make a difference. If you want to express in numbers, this is the NTT, which is sort of public health expression of how powerful a treatment is, is 1.7. It means that if you treat -- you need to treat only on average 1.7 children in order to add one to those who will improve regardless of a treatment. So if you imagine to treat 1.7 children, 0.7 will improve by itself without the treatment, and one will improve because of risperidone. That is a very high number needed to treat. That is much greater than an antibiotic, for instance. For instance antibiotic for an ear infection has a number needed to treat of 5 or 6. So of 5 kids you treat for otitis media, 4 will improve spontaneously. Without antibiotic, only one would be because of the addition of the antibiotic. There are significant side effects. Discontinuation results in relapse, but not in all cases. Unfortunately, we don't we know which subjects again. Again, you know, if you

want, you can take a look at the paper. You can stay tuned, because these analyses are also coming out and will be out in the next few months. Thank you.

Dr. Insel: Thank you, Ben. How about questions or comments?

Dr. Zeph: Are there any data around long- term use? I know in this particular study you said that you had to stop following them or you had to stop the study. Is there any attempt to follow in terms of long-term use?

Dr. Vitiello: Yes. When at the end of six months basically the patients were discharged to the community, so it was up to the clinician to continue treatment or not. We are in the process of rechecking these patients and reassessing them one year after discharge from the study to see how many are still in treatment, what their experience was, why they discontinued treatment. We have so far data on about 70 percent of them. So in the next few months probably we will -- we are trying to get at least 80, 90 percent of information on the subject.

Dr. Carbone: Now that you have these very encouraging clinical data, are there any plans to sort of advance to either something more mechanistic or trying to look for changes in markers of some sort, functional MRIs, serotonin metabolism, dopamine metabolism, anything that would lead you to a better feeling of mechanism? Typically, sometimes you start with Drug A and it's somewhat effective, but you can refine the drug with more information to become more effective the next generation.

Dr. Vitiello: We are not directly doing that because the purpose of RUPP basically is to test treatment that are used off label or in the community. But I think what you're suggesting is very important. It probably is the only way to go, meaning not to have a palliative improvement only but to go to the core of autism, and I'm very interested in that. Actually in about one year ago, we had a workshop here in Bethesda focused on Fragile X. This is connected back to the discussion we had before. And to say since we know for Fragile X what the gene is, we know what the

protein there, you know, what can be done with this information instead of just saying fine, you know, we have hit one disorder? How can we apply that information as a prototype for genetic therapy? And so we tried to steer activity in that. But again, I don't know how much is going on right now.

Dr. Insel: Just to follow up on that question, we know that the atypical antipsychotics differ in terms of their in vitro pharmacology. Is there any evidence that risperidone, for instance, would be different than any of the other compounds based on just even anecdotal clinical experience? Dr. Vitiello: There have been studies on alanzapine, for instance. As far as I know, no. I don't have. Certainly risperidone is probably the more typical of the atypical, and there are other atypical that are more atypical. But I don't know if this translates into a differential, more targeted efficacy for children with autism.

Voice: Along the same lines having to do with the side effects, could it be that some of the other atypicals might be less likely to cause the

obesity? Are there an interventions that are good for planning for that and trying to keep that side effect down?

Dr. Vitiello: Yes. There are atypicals that don't have the weight gain, like ziprasidone, for instance, already on the market, and aripeprizole is coming on the market now. So those drugs could be worth looking at just because they seem to have, not to have the weight gain problem.

Voice: Also, there was a paper just this month or last month in Developmental Medicine Child Neurology by Dr. DeLong at Duke about -- he's been studying Prozac or fluoxetine for a long time, and particularly in children whose families have a high incidence of other affective disorders. Children with autism whose families have affective disorders. And he feels strongly that there is a link there, in terms of getting back to the question about the genetics. And I think that's an interesting question.

Dr. Vitiello: I don't know the paper. I will take a look.

Dr. Insel: One final question. It's actually kind of a sensitive issue, but I'd like to maybe get both your thoughts and Dr. Carbone's thoughts about this. We know from the educational intervention perspective that the earlier you intervene, the more likely the beneficial effects will be and the more long-lasting. I don't know how comfortable people are in giving risperidone to children at a very young age, right after they have been diagnosed. But it looked like the mean age in the study that you cited is about 8 or 9 years.

Dr. Vitiello: Eight, yes.

Dr. Insel: So is there, again, experience at all with intervening at a much earlier time pharmacologically to find out whether there is a greater benefit or perhaps even a worse outcome by doing that? Dr. Vitiello: It's a very important question that can only be answered with long-term follow-up and treatment. On the short term, we look at age as a possible moderator of treatment, and we found it was not a significant moderator, meaning that both the young and the old kids

tended to respond pretty much in the same way, even though the younger for some reason have a slightly greater placebo response, but it was sort of a trend.

Dr. Cordero: A follow-up to your questions. I think one of the questions in a study like this is whether in fact the drug is having an impact or an effect on the disease itself, or really on the secondary conditions and complications that these children are having. Especially when I think you have something like 30 percent of this group have moderate to severe MR, one wonders whether this is really sort of a typical child with autism or it's just a subgroup. So I think that's really an important question to try to figure out.

Dr. Carbone: You probably know more than I do about this, but I was discussing with Dr. Lind at Hopkins, she had some interesting paradigms for pre-verbal testing, eye contact, et cetera. And the question would be -- there are sort of several questions. But one might be very simplistic of short term. In other words, load a child, give them enough drug to be confident that you'll have

an effect maybe even literally for days, and measure a short-term outcome. Do you get an improvement in a particular autism, pre-verbal autism indicator? Because I think that kind of a study -- now don't quote me that the FDA would approve that, okay? [Laughter.]

Dr. Carbone: I'm not speaking as an FDA person. But, for example, from a risk point of view, that may be perceived as a smaller risk than say a several month trial on an infant, at least to get some data that advancing to longer therapy might be of value. And I think the type of drugs one picks might be different based on trying to heal the damaged brain versus protect a being damaged brain. But I think we're well out of our understanding of autism at that point.

Dr. Kallen: I think the RUPP study is to be commended for the design and the execution of the study. This is exactly a model of how it should be done. Unfortunately, there may never be a treatment for autism in the medical sense. And one of the things that we really don't understand, because we don't understand autism, is really

what's happening at the micro level, the micro environment in the brain when you're using a psychopharmaceutical therapeutic agent in terms of receptor turnover, effects on synthesis of new transmitters, how they're released, effects on messenger RNA or whatever. There's so much there in a black box that we don't understand that could be very important in terms of how the brain is remodeled in terms of learning if one is using ABA or whatever. We're hoping that the network of dendritic processes or whatever are reinforced in those pathways that need to be reinforced and regressed, and others that are not the favored pathways. We are literally flying blind. But the cautionary note is what are the long-term effects of these medications on a young, developing brain, albeit a brain that has significant problems?

Dr. Insel: A last comment from Barry.

Dr. Gordon: Actually, this is in response to yours, not to comment on yours. Were you alluding, Tom, to the prophylactic treatment of schizophrenia development study? And if so, how has that been turning out, or is it too early to

say? Because that's the model in a sense you were bringing up. Namely, we think we have an effective drug. Maybe if we hit before the children become symptomatic, it'll be better.

Dr. Insel: That's the model. Actually I don't know what the results of that look like. Richard may know more about that than I do. I think that's at a very, very early phase. I don't think there are any results, certainly nothing has been published and a lot has been talked about. But I don't think we're at the stage of actually having numbers to look at.

Dr. Nakamura: NIMH has decided it would not sponsor those studies because of the ethical question about treating individuals who may not ever develop symptoms of schizophrenia. Most of the studies that we're looking at right now are trying to intervene as early as possible after the initiation of symptoms rather than that. Though I know there are individuals looking at the question of prodromal symptom evaluation.

DR INSEL: Would you like to comment, Ben?

Dr. Vitiello: Yes. There is actually a report in the archives of General Psychiatry I think this month or the previous month by Patrick McGrory from Melbourne in Australia. You randomize basically adolescents or young adults who have so-called prodrome, meaning that they get symptoms of you would say incipient psychosis almost because of their disorganization even though they didn't have fully criteria for schizophrenia. Randomize either to take a low dose of risperidone or just management in the community. And he is reporting on a trend toward a little better prognosis event of I think it was two years. But it's very subtle. The sample is small. I found that it was not really a convincing study yet.

Dr. Insel: Okay. I think we need to move along. The final session will be an opportunity for public comment. Rick Rollens is the first in line and perhaps not surprisingly, but we're all looking forward to hearing from you. You didn't have a chance to say what you wanted to earlier, so this is a good opportunity.

Dr. Rollens: I do appreciate that. I don't think -- we would be terribly remiss as an organization and I think as an autism community of all the people here today and parents throughout the country and everyone who is dedicated to finding the causes and cures for autism to not recognize the wonderful addition of Dr. Tom Insel as the new director of NIMH. I think one of the best things that's happened to this field is your taking that position. [Applause.]

Dr. Rollens: Now you'll let me talk when I get up the next time. [Laughter.]

Dr. Rollens: Secondly, another point I just wanted to make, I think all of us kind of take away from this meeting that we're not doing a very good job of really subtyping autism. And again, you know, we see these results from various studies and tests. It doesn't matter if it's a clinical intervention or a biological research program, but we keep getting mixed results. And I think a real priority for all of us, and I know at the M.I.N.D. Institute we're adopting this philosophy of doing a much better job of subtyping

and sub-classing autism. Thirdly, I just wanted to mention on the screening issue that we need to be doing a much better job getting people who are capable of diagnosing autism and pediatricians to diagnose autism when they see it and not to delay the diagnosis. This is a major problem in the community. Every day all of us see children that we know are on the spectrum or have level one autism, but there's a general feeling in many parts of the country particularly that if we just wait and see if this child grows out of this condition then it's better than telling the parents that the child might be at risk. And lastly, a little bit about the autism epidemic and its effect on services. During the break, one of the good things that happened when I wasn't able to speak when I was first up here is I got on the telephone during the break and called the director of the Department of Developmental Services in California to get an age breakdown of the number of cases of California and who are these cases. And I think you'll find these numbers absolutely shocking. Keep in mind in California we have an

early start program, zero to three kids are put in an early start program. We only have .07 percent of our total number of cases of kids zero to two, so we're not talking when we report these new numbers of cases of any children really under the age of three years old, a very small number of children in the zero to two groups. When you add up the numbers, 50 percent of all the cases of autism, level one autism, not including PDD, NOS or Asperger's, are under the age of nine years old. Fifty percent. You move it up the next notch, two out of three children are within the ages of zero to 13 years old. Move it up another notch, you move it to 80 percent of the folks who were born after 1980 or are under the age of 21. So in a system where we've had a difficult time up to this date of trying to provide services for adults, we only have less than 3,000 adults with autism in California. We're adding more than 3,000 new cases of children every year to California's developmental services system. This is one state and one set of a data from a system that's been around since 1969. So if we thought we had

problems providing services for adults today, the picture is pretty clear. Thank you.

Dr. Insel: Go ahead.

Ms. Ruppmann: I wanted to share some information and an invitation to you, and that's why I called ahead and said can I bring my stuff and they said yeah, but bring 80 copies. So I schlepped these on the Metro, and my husband dropped me off at the station at 7:30 this morning, and by gum, I'm handing them out.

Dr. Insel: Can you identify yourself so we'll all know –

Ms. Ruppmann: Yes. I'm Jamie Ruppmann and I'm the parent of a 31-year-old son who has autism, and I'm Director of Governmental Relations for TASH, which is a 25-year-old organization, an advocacy and human rights and civil rights organization representing people with the most significant levels of disability. I'm also the past Government Affairs Director of the Autism Society of America, and the past president of the Virginia Autism Society of America chapter. So I'm an old mom who's been around a very long time. We

received funding, TASH did, from the Nancy Lurie Marks Family Foundation to bring together a group of adults who have the label of autism, some who have verbal communication, some who use various forms of augmentative communication, some, yes, who use facilitated communication and require support for typing. We met with them in May of this year in Boston, and it was quite an interesting and powerful day. The subject was public policy and how it affects the lives of individuals and the growing increasing power of people with disabilities in making public policy and in utilizing public policy to improve their lives in ways that they direct, and were in fact people with autism interested in becoming part of that movement, and did they have something to say about that. And we found that they had a lot to say about that. And the outcome of that is in our TASH Connection, which we tried to report out. If you'll hand those around -- we tried to report out as to just as fast as we could get things written down and recorded and said, what folks had to say about their lives, because they had very

meaningful and as you can imagine, very poignant things to tell us. And that was not a surprise. I have to in full disclosure I will tell you that this nice looking guy right here that says choose to work, that's my son Stephan. That's at an employment rally summer before last, and he was asked to be a speaker. This man here, this handsome man, 31-year- old man, didn't have verbal language until he was almost eight years old. He was eight years old and he had never come to us and asked us a question or made a declarative statement. So it's a big day for us when he stands up in front of a large group of people on the grounds of the Capitol to talk about what it means to him to be employed and how he feels about that and what his feelings are about a self- determined life. We are following up -- this is the point of introducing myself to you -- we will be following up at our TASH National Conference with two more meetings. John O'Brien is coming up to meet with our folks who have autism, and we've increased that group. This is a larger group of adults now. He's going to be working with them on Tuesday,

December the 10th, and they're going to be finalizing and really firming up some of their vision that they worked on in May. And then on Wednesday, I'd like to invite everyone here, because I know of your commitment, as many of you who might be able to come or come to represent your organizations or agencies, to a meeting that we're going to have to really set up a dialogue to talk about what are the barriers to people with autism really becoming part of that self-determining group of adults with disabilities who are making such a difference in terms of the direction that our government and our Congress is taking when they start looking at services and supports. And I think because of the emphasis today and our concern about our adults, their futures, their retirement, and our young adults coming out of our school settings into relatively a void for services, I think the idea that they could partner with us to begin to set that agenda, to begin to help us as their parents and researchers and service providers to set that agenda on what those services should look like and

what they really need and want in their lives. I think that we probably think we know all that they want and need, but they told us in no uncertain terms that they felt that we were underestimating them. And I think there have been many stories here today about expectations. And we had a very interesting sort of a revolution among that group of folks. I think this is a conversation you would enjoy, and we encourage you to think about coming. That was my message today and also to thank you so very much. I'm a very old mom, and some of this I've heard, and some of this we've been working on a very long time. It encourages me, on the one hand, but discourages me on the other hand and almost makes me feel like I need to apologize maybe to the younger families to say that, you know, we've worked very hard over these years since our children were diagnosed, and still so much of it we haven't fixed. Still so much of it we're discussing. Still. And yet we know what the potential can be for our kids. So, on the one hand you have a feeling of sadness, and on the other, great hope for the future. Because this parent

movement has become extremely powerful. I was part of that generation of parents who did the first knocking on the door to say parents are your partners. Parents are the power here. Parents and people with disabilities are going to make the difference. You need us. And I think today is really proof that we were right. That the partnership and the collaboration between the research and practice and families and people with disabilities is going to be what makes the difference. So I have no doubt in mind that within ten years we'll be having a completely different meeting. So, God bless all of you in your endeavors, and thanks so much for having such a good meeting today. And here are some more invitations. Thank you.

Dr. Insel: Thank you. I think we need each other actually. Other comments?

Ms. Polinsky: Hello. My name is Bernice Polinsky. I'm from Long Island with Pat Schissel. And I'm nervous because I'm not used to standing in front of a microphone. But anyway, I just wanted to continue with the discussion about 3,000

people who are adults in California with diagnosis and just to explain the reason why there's only 3,000 people with that diagnosis is because they're getting the wrong diagnosis or they're not getting diagnosis. And people are afraid to give the diagnosis or they're in hospitals with a mental health diagnosis. They're dropping out of colleges. They're not getting jobs. I co-facilitate with Linda Geller from the Cody Center a support group for parents of older teens and adults, and every day we're getting phone calls from parents of adults and teenagers who just got that diagnosis. They're falling through the cracks. The numbers are increasing immensely, and it's because of the increase in these children and adults that we're seeing large numbers in addition to every other reason that we're hearing. That's one of the major reasons. And we're very, very happy that you're doing this research. And we're very happy to explain also that great numbers are because of the adults that are being diagnosed.

Dr. Insel: Thank you.

Ms. Chase: Again, thank you. As everyone else said, this has been quite an eye opener for me, because this is I guess one of my very first opportunities to be among the professionals that are doing the research, and I thank you so much.
Dr. Insel: For the purposes of our tape, it would be good if you could identify yourself.

Ms. Chase: I'm so sorry. Hi. I'm Shari Chase. And as I mentioned before, I'm the mother of a six-year-old boy who is diagnosed with autism, and there are three points I just wanted to make. One, I'm hoping that there will be more emphasis put on the environmental issues. My son, my whole family was poisoned by arsenic through a lawn product, and as I said before, his development had been completely followed up to, I had said 18 months before, but it actually was 20 months. And through testing of myself, we all started off by losing our reflexes and our feeling in our hands and feet which normally children with autism don't have that experience. It's been four years now and last May he finally got his reflexes back. But as a result, he was developing normally, he has autism.

There are many skills that he has that are atypical of a child with autism, as his doctors have said, that he does have. That said, I just really would like to emphasize that I hope the environmental issues such as heavy metals and pesticides is not overlooked in the research, because that's something we could do. We would work on that. That isn't something where we have to look into an animal's brain. I mean, I guess we do. We have to see the effects. But if it's proven or if they look into the fact that children, the reason we're having such high increases is by having exposures to pesticides and heavy metals, then we can stop that exposure, and then we could look and if there's anything, any pathways that can be changed in those children's brains to try to improve them. And I think it would lessen the amounts of research that has to go in and we could get to the heart of the crux of the problem. So, again, I would hope that you all as researchers will look towards that and not only put all your eggs in one basket with the genetics. I'm not saying that my son possibly was genetically

predisposed. I think there is a straw that breaks the camel's back. So that said, that was one thing I wanted to mention. The second thing with the diagnosis, I think there's a lot more children that we're not hearing about that had the diagnosis of autism, and the reason we're not hearing about it is, such as my insurance company. I had a phone call from my insurance company when my son's medical records went into them that I needed to go back to the doctor and get everything stripped from his records that were autistic because they would stop covering him for any medical coverage such as speech therapy, occupational therapy, developmental. So I did that. He's still autistic. He's no different than he was the day before, but the assistant to the medical director of my insurance company was kind enough to do that, because she said, you know what? I have an autistic son, and you will not be able to pay for this out of your pocket. And I think that there's a lot more children that are autistic. So that's a second issue I wanted to bring up that something needs to be changed with

the insurance companies. And the third item I wanted to bring up is I'm not exactly sure -- did you say this? That if you do not search for it you will not find what you don't look for? Lucille had said that. Well, in addition to that, if we as parents, researchers, teachers do not appreciate what it's like to be autistic, then it's very difficult for us to appreciate what needs to be done for them with the interventions. And there was a fabulous video, and unfortunately, the name of it escapes me, but I would be more than happy to find out, that in Howard County, Maryland, the teachers are required to observe. And what it is is there is a group of teachers who are put in a room and they are put through different types of work skills, such as -- Fat City. That's exactly what it is. Every single person needs to see it. I think we need to all go through that training. But if we all see it, we could suddenly appreciate what it's like to be autistic. One example is I went to a seminar and they had us all put on snow gloves, and we had to button and unbutton our jackets. You can't button and unbutton your jacket

with snow gloves on. If you can relate that your brain, looking at instructions on a sheet, and if the processing, everything is going like that, that child can't focus on that. Well, anyway, that said, if all of you can somehow get your hands on Fat City, and that might be a very good public information source, because if that's required not only for the teachers to see and health care providers to see, but if it's something that's put on TV, maybe CNN could put it on or whatever, it will just suddenly open a lot of people's eyes. So with all that said, I thank you again so much. I'm new to this, but you will see me for the rest of my life campaigning and trying to find whatever funds I can to help you all do your work, and God bless you all.

Dr. Insel: Thank you. Other comments? [Pause.] This is a surprisingly quiet and non-contentious group.

Voice: Well, since you asked.

Dr. Insel: That was a challenge. That was a challenge.

Ms. Schissel: One of the problems that I find, I run a support group also, but for the school-age kids, if you can take one child, send them to four different doctors and you'll have four different diagnoses, which is very confusing. I don't know what any of you can do about that. But there's not any consistency. And it makes it very difficult and very confusing within all of the communities. We're on Long Island, and the school classification has to be autism. It's most helpful for a school classification. In New York City, that's absolutely a classification you can't have, because you'd be going into a class for mentally retarded. I don't know what happens in other states, but there's no consistency across the country. So we're in Washington, and I work with a bureaucracy in a school system, and I feel as a Board of Education member I have a lot of, you know, control at that level. So I have no idea at this level what you can do. But the consistency is so helpful. On Long Island, on a state level I know it's difficult. On a national level I'm sure it's that much more difficult. But if there's some

consistency that can come top down in terms of diagnoses, in terms of school classifications doing that would be so helpful to parents. First of all, obviously the A word is like the C word was in the fifties, which is a big problem. So what we do on the support group level is stop that immediately and help parents get used to the word autism, so that's helpful and we're all doing that here. And those are the kinds of things. Okay. So I wasn't quiet.

Dr. Insel: Thank you very much. Barry?

Dr. Gordon: I'd like to comment on that. I'm a physician and I'm also a parent, and we run into issues of coding all the time. And frequently we discovered that the physicians often agree on what's there, but they disagree on just how to weight it and how to force it into some of the categories they have. So some of that difference that you hear often doesn't exist at the level of data description and behavior. It differs I think at the level of just how much weight and how much confidence or unconfidence the person will have in telling you something, giving an answer. And we

also saw that the medical diagnosis doesn't have anything to do with the educational/social/political diagnosis at all. And as one of the I think you mentioned the coding where somebody was told to strip it out from the diagnosis for the insurance not covering it, I think we've seen the same thing in the education level where different educational systems will take the same medical records and code them somewhat differently, much to our surprise. And I don't know if there is a solution for that except to recognize that it occurs at several different levels. That there's a medical level where there's disagreements and there's an educational coding level where there's also disagreements, and then there's an insurance level that will probably disagree with everything.

Dr. Vitiello: But there are the technical instruments to solve this disagreement. There are validated interviews with the parents that has been found to be reliable and valid. It requires training, like autism diagnostic interview that was developed by Michael Ratar and another

researcher here in the United States like Ettie Lord. In some ways, if one wants a good quality diagnosis that has good validity, it is possible. The means exist. It's just a matter of applying them to the community.

Dr. Gordon: I wasn't denying that. In fact, I know that the ADOS, the ADI have tremendous reliability and stability and in fact have been extended down to a fairly young age. The problem of course, and I would let others address that, is it doesn't seem practical for people to use them. It takes an intensive training session to become reliable in them. Nobody has such people waiting around for the autistic individual to show up. And I don't know what mechanism the U.S. health care system would have for funneling all the potential children that might be diagnosed into specialized centers where that could be done with a greater reliability.

Dr. Rice: I'd like to speak to the issue. In terms of the data, it's certainly one thing –

Dr. Insel: Could you also identify yourself?

Dr. Rice: Oh, I'm sorry. Cathy Rice from the CDC. In terms of getting consistency within community diagnosis, that's certainly a challenge. We may have some data in the CDC surveillance studies that we're doing that can speak to this issue int he future as we collect surveillance data on the incidence and prevalence of autism. We're looking at behavioral descriptors. We're using diagnostic codes and educational classifications as a way of identifying kids. But we're not only looking at kids who have a previous autism spectrum diagnosis or classification, then we can look at kids that clearly have the behavioral patterns associated with autism but weren't labeled that. So in the future, we should have some data that will help at least inform this discussion a little bit.

Dr. Rollens: In a system in California that's been in place since 1969 in dealing with developmental disabilities such as mental retardation, cerebral palsy, autism and epilepsy, there's always a concern about is the diagnosis correct. And again, in our system, it's an

exclusive system. That is, if you don't meet what is considered level one autism, which is the DSM for autism, then you are not qualified for services. You're not added to the system. That does not include PDD, NOS, Asperger's or any of the other autism spectrum disorders. So the $1 million, three-year study that was just released a couple of weeks ago out of the M.I.N.D. Institute went back as one of the factors to look at are we getting this diagnostic issue right? Are in fact these numbers that the Department of Developmental Services is producing every quarter about the number of new cases, is it in fact autism or are we calling it something else or called it something else in the past? They went back and rediagnosed these kids using ADI and ADOS and in fact found an 85 to 90 percent accuracy rate on in fact the kids that were called level one autism cases were in fact kids with level one autism according to ADOS and ADI. So if anything, I think we're missing -- the numbers out there are clearly larger I can say in our state when you're not including the entire spectrum of autism, including

PDD, NOS and Asperger's in these numbers, and these horrific numbers that we're seeing which now autism is the number one disability coming into California's developmental services system. It's gone from a 3 percent of the total number of intakes to 40 percent over a 20-year period. This is like absolutely shocking to the folks in our system and in our state who've been around since the inception of our system in 1969.

Dr. Insel: I'm beginning to feel that it's been a very long day. People are starting to look a little bit worn at the edges. It may be time for us to wrap this up. I think in summary, if I can take just a moment, I found this discussion really very hopeful, but I think as the day went on, it became clearer that we have the makings here of really a working group, not just a group that will be convened based on some mandate. I think there's a real interest here in getting some things done. And it sounds to me like the subcommittees will be a very helpful part of that process. The next meeting is tentatively scheduled for May 13th. We may need to reschedule because of a possible

conflict with the CPEA meeting. But if we can do it, we'll shoot for May 13th. In the interim, the hope is that the subcommittees will continue to work together and that we can use that meeting really just as an update on their progress. We're available to help in any way that we can. We'd like to be able to use the Web site to at least provide the records of everything that's taken place at this meeting, including the Powerpoint slides and any of the documents that are relevant we'll try to maintain some links to. It would be helpful in the next few weeks if you have particular items that you would like to have on the agenda of the next meeting if we could have those brought up fairly soon and we can try to schedule that. And any other suggestions you have. In fact, if we have a minute now, if there are suggestions you have for the format of the meeting, we might take a moment to listen to that as well and try to make this meeting as useful as possible. Any particular strong feelings about that? Should we plan the next one much along the lines of this one with updates, progress reports

and some new findings as they come out so people know about them? [No response.]

Dr. Insel: And then the real challenge is to make sure, particularly in the services arena, that we have people talking across agencies that we know about what the options are for things that can be done collaboratively. We will try to make sure that next time we have someone from the Medicare/Medicaid program from CMS who can help us with some of the details of that as well. If there are no other comments, I'd like to thank everyone who participated today, and particularly those of you who came from far away. We really appreciate your taking the time and the effort. And those of you who were available for public comment, extremely helpful. That's right. I think Lee Grossman gets the record for coming the furthest.

Mr. Grossman: I always win this and the prize always is a round trip to Hawaii. [Laughter.]

Dr. Insel: There has been a recommendation that the next meeting be held in Hawaii.

Mr. Grossman: It definitely works for me.

Dr. Insel: Maybe it will be a subsequent one. Thanks to everyone for participating. [Whereupon, at 4:55 p.m. on Friday, November 22, 2002, the Interagency Autism Coordinating Committee Meeting adjourned.]