

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS
ADVISORY COMMITTEE

VOLUME I

Tuesday, March 13, 2001

8:00 a.m.

Holiday Inn Gaithersburg
Two Montgomery Village Avenue
Gaithersburg, Maryland

PARTICIPANTS

Claudia H. Kawas, M.D., Consultant and Acting Chairperson
Sandra Titus, Executive Secretary

MEMBERS:

LaRoy P. Penix, M.D.
Gerald Van Belle, Ph.D.
Howard L. Weiner, M.D.
Michael Grundman, M.D., M.P.H.
Jerry S. Wolinsky, M.D.

INVITED SPEAKERS:

Helena Chui, M.D.
Steven DeKosky, M.D.
Ranjan Duara, M.D.
Steven Ferris, M.D.
Mary Ganguli, M.D.
Ronald Petersen, M.D., Ph.D.

PUBLIC SPEAKERS:

Dr. Barry Reisberg
Dr. Tony Waegeman
Dr. Yogesh Shah

FDA:

Robert Temple, M.D.
Russell Katz, M.D.
Ranjit Mani, M.D.

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1 P R O C E E D I N G S

2 Call to Order and Introductions

3 DR. KAWAS: Good morning, and welcome to our
4 meeting of the Peripheral and Central Nervous System Drug
5 Advisory Committee. My name is Claudia Kawas. I am from
6 the University of California at Irvine, and we will now call
7 the meeting to order.

8 If we can begin first with introductions so
9 everyone will know who is seated around the table, perhaps
10 we can start with the FDA in the corner. Dr. Katz?

11 DR. KATZ: Russ Katz, Division of
12 Neuropharmacological Drug Products at the agency.

13 DR. MANI: Ranjit Mani, Division of Neuropharm.

14 DR. PENIX: LaRoy Penix, Moorehouse School of
15 Medicine, Neuroscience Institute.

16 DR. VAN BELLE: Gerald Van Belle, University of
17 Washington in Seattle.

18 DR. WEINER: Howard Weiner, Brigham and Women's
19 Hospital, Harvard Medical School.

20 DR. WOLINSKY: Jerry Wolinsky, University of
21 Texas, Houston.

22 DR. GRUNDMAN: Michael Grundman, University of
23 California, San Diego.

24 DR. TITUS: Sandy Titus, the FDA. I am the
25 executive secretary for this committee.

1 DR. PETERSEN: Ron Petersen, Mayo Clinic,
2 Rochester, Minnesota.

3 DR. GANGULI: Mary Ganguli, University of
4 Pittsburgh.

5 DR. DUARA: Ranjan Duara, University of Miami
6 School of Medicine.

7 DR. DEKOSKY: Steven DeKosky, University of
8 Pittsburgh.

9 DR. FERRIS: Steven Ferris, New York University
10 School of Medicine.

11 DR. KAWAS: Thank you very much. I think we have
12 a very interesting day. We will now let Dr. Titus read the
13 conflict of interest statement.

14 Conflict of Interest Statement

15 DR. TITUS: The following announcement addresses
16 the issue of conflict of interest with regard to this
17 meeting and is made a part of the record to preclude even
18 the appearance of such at this meeting.

19 Based on the submitted agenda for the meeting and
20 all financial interests reported by the committee
21 participants, it has been determined that all interests in
22 firms regulated by the Center for Drug Evaluation and
23 Research which have been reported by the participants
24 present no potential for an appearance of a conflict of
25 interest at this meeting with the following exceptions:

1 Since the issue to be discussed by the committee at this
2 meeting will not have a unique impact on any particular firm
3 or product but, rather, may have widespread implications
4 with respect to an entire class of products, in accordance
5 with USC 208(b), each participant has been granted a waiver
6 which permits them to participate in today's discussions.

7 A copy of these waiver statements may be obtained
8 by submitting a written request to agency's Freedom of
9 Information Office, Room 12A-30 of the Parklawn Building.

10 With respect to FDA's invited guests, there are
11 reported interests which we believe should be made public to
12 allow the participants to objectively evaluate their
13 comments. Dr. Ronald Petersen would like to disclose that
14 he is project director on a National Institute of Aging
15 grant which is supported by Pfizer, Eisai and Roche
16 Vitamins.

17 Dr. Philip Gorelick would like to disclose that he
18 has two NIH grants. Roche Laboratories and Bayer supplies
19 the medication for each of these grants. In addition, he is
20 on the speaker bureaus for Janssen/Excerpta Medica, Dupont,
21 Roche Laboratories, Bristol Myers Squibb and Boehringer
22 Ingelheim. Dr. Gorelick has consultant agreements with NPS,
23 Eisai, G.D. Searle/Lorex, Roche Laboratories, Ketchum,
24 AstraZeneca, Glaxo Wellcome, Warner-Lambert, Baxter, Rand,
25 Solvay Pharmaceutical and Consumer Healthcare Products

1 Association. He is also on the Through Leader Panel which
2 is supported by the Weinberg Group.

3 Dr. Ranjan Duara would like to disclose that he is
4 an investigator on a study entitled Validations of a Memory
5 Screening Instrument. The study is supported by a contract
6 from Pfizer. He also serves as a scientific advisor for
7 Pfizer/Eisai, Novartis and Janssen.

8 Dr. Steven DeKosky would like to report that he
9 owns stock in Cephalon. He is a research investigator for
10 Eisai-Pfizer, Novartis, and Schwabe. In addition, Dr.
11 DeKosky consults for Pfizer, Cephalon, Schwabe, Janssen,
12 Novartis, AstraZeneca and Eli Lilly, and serves as a speaker
13 for Novartis.

14 Finally, Dr. Mary Ganguli would like to report
15 that she is a researcher for the National Institutes of
16 Health.

17 In the event that the discussions involve any
18 other products or firms not already on the agenda for which
19 an FDA participant has a financial interest, the
20 participants are aware of the need to exclude themselves
21 from such involvement and their exclusions will be noted for
22 the record.

23 With respect to all other participants, we ask in
24 the interest of fairness that they address any current or
25 previous financial involvement with any firm whose products

1 they may wish to comment upon. Thank you.

2 DR. KAWAS: Thank you, Dr. Titus. I think Dr.
3 Temple just joined us. Maybe we can let him introduce
4 himself.

5 DR. TEMPLE: I am Dr. Temple. I am director of
6 this Office in which Neuropharm is.

7 DR. KAWAS: This committee was convened in order
8 to discuss the topic of MCI or mild cognitive impairment.
9 We have an awful lot of material that is going to be
10 presented today by an awful lot of people. I am told I am
11 supposed to be up here with a timer that has fifteen minutes
12 for each of you to speak and five minutes of questions, and
13 that is going to be the challenge of the day. There is a
14 light up there for the speakers. You will have a two-minute
15 warning when the light will become yellow. After that Sandy
16 gets up on the table and starts making signs if you go
17 beyond.

18 I wanted us to have a lot of time for discussion.
19 So, we are going to try and keep the presentations as much
20 on schedule as possible, realizing that some of the
21 discussion might happen in the middle of presentations. By
22 unanimous opinion and coercion, Dr. Ron Petersen has been
23 moved into the first speaker slot. So, without further ado,
24 Dr. Petersen, Mayo Clinic, Department of Neurology. Oh, we
25 left out Dr. Katz.

1 [Laughter]

2 We really do want to give FDA their time to tell
3 us our mission for today. So, Dr. Russell Katz?

4 Welcome and FDA Overview of Issues

5 DR. KATZ: First of all, good morning. I would
6 like to welcome the committee to this meeting, the PCNS
7 advisory committee. I would particularly like to extend an
8 additional welcome to our invited guests who have agreed to
9 graciously give their time and their expertise to help us
10 out this morning. Let me also thank Sandy Titus for
11 arranging the meeting, and I would particularly let me thank
12 explicitly Dr. Ranjit Mani, a medical reviewer in the
13 Division, who is sitting at the table, who really pretty
14 much put the meeting together, identified the experts who
15 are here today, invited them, and pretty much wrote the
16 briefing memo in the books that you have received for
17 today's and tomorrow's meeting. So, thanks, Ranjit.

18 We are actually presenting you with a fairly
19 unusual problem today. Ordinarily we would bring to the
20 committee a particular application for a new drug and we
21 would ask you to interpret the data and help us out there,
22 but today we are asking you a very different sort of
23 question, a more difficult question, it seems to me. We are
24 asking you to address some fundamental aspects of a
25 particular diagnosis to help us characterize, decide if it

1 exists and how best it ought to be studied. That is unusual
2 and we know it is difficult.

3 The reason we are asking now is because a number
4 of pharmaceutical sponsors have approached the Division,
5 asking to develop treatments for mild cognitive impairment
6 or MCI. MCI, as you know, has been characterized variously
7 in the literature but, in general, it is a condition that is
8 described as occurring in elderly patients who predominantly
9 have a memory impairment, some slight cognitive impairment
10 perhaps and some minimal dysfunction in their daily
11 functioning, although that is generally relatively intact,
12 and patients are considered neither to be normal nor to have
13 dementia but their cognitive status falls somewhere in
14 between.

15 Most of the trials that the sponsors have come to
16 us with have identified as a primary measure of drug effect
17 time to progression to Alzheimer's disease, although some of
18 them look strictly at the symptoms of MCI. We have let
19 these trials proceed but we have told all sponsors that we
20 will not make any commitments as far as interpreting the
21 data pending a wider discussion of some of these more
22 fundamental questions that I hope we will work out or at
23 least discuss today.

24 By way of background, let me just say that the
25 Federal Food, Drug and Cosmetic Act, which is the statute

1 under which we regulate drugs, requires that in order for a
2 new drug to be approved the sponsor must submit what is
3 called substantial evidence of effectiveness that the
4 treatment will have the effect represented for it in product
5 labeling. It is important to understand that a product's
6 approval is inextricably linked to the language that is used
7 in product labeling. I say this because one of the most
8 critical factors that we need to consider when we are
9 considering approving a drug and, therefore, writing
10 labeling for it is whether or not the population for whom
11 the drug is intended can be unambiguously described.

12 So, that takes us to the first question we would
13 like you to think about. In the case of MCI there is not
14 unanimity in the literature about the diagnostic criteria
15 that can reliably identify patients who are alleged to have
16 the condition. So, as I say, one of the critical questions
17 we would like you to address is whether or not you believe
18 that there do exist a set of criteria that can be readily
19 applied by practitioners and that can reproducibly and
20 reliably identify patients presumed to have MCI.

21 Ordinarily, diagnostic criteria are ideally
22 compared to a gold standard to decide how specific and
23 sensitive they are. Obviously, for example, in Alzheimer's
24 disease the clinical criteria can be validated against the
25 pathologic findings and they do pretty well, as you know,

1 against those. But, given the nature of MCI, there isn't
2 this wide, robust pathologic database against which to
3 compare the diagnostic criteria. So, that is a particular
4 complication here.

5 Even if you find that there is a specific set of
6 diagnostic criteria that can reliably identify patients as
7 having MCI, there is another very critical question we would
8 like you to address, and I guess it will take up a good part
9 of the discussion this afternoon. In longitudinal studies
10 of patients diagnosed with MCI, a substantial proportion of
11 those patients go on to progress to frank Alzheimer's
12 disease, and I expect that later today we will hear various
13 estimates about the probability of that happening in these
14 cohorts. In addition, static and functional imaging studies
15 in patients diagnosed with MCI reveal changes that are
16 basically qualitatively similar to those seen in Alzheimer's
17 patients, though quantitatively much less severe, and the
18 few pathologic studies that have been done in these patients
19 also reveal qualitatively similar changes as those seen in
20 patients with Alzheimer's disease.

21 These factors, taken together, suggest that MCI
22 may, in fact, just simply be early Alzheimer's disease in
23 patients who have not yet progressed to the point where they
24 meet the formal, accepted clinical criteria for making that
25 diagnosis. So, we are particularly interested in your views

1 on whether or not you think MCI really is just early
2 Alzheimer's disease. It is critical because if it is early
3 Alzheimer's disease it would be inappropriate to grant a
4 claim for the indication of MCI when, in fact, it really is
5 something else.

6 As you probably know, currently there are four
7 approved treatments for Alzheimer's disease and for what we
8 call mild to moderate Alzheimer's disease, and it is fair to
9 ask if a drug is shown to be effective in patients diagnosed
10 we MCI, if that is fundamentally different from the claims
11 that we have already granted to these four drugs.

12 In fact, as I said earlier, the trial design that
13 we have most commonly seen for these patients looks, as a
14 primary measure of drug effectiveness, at time to diagnosis
15 of Alzheimer's disease. So, that design itself could be
16 taken to suggest that, in fact, these patients really just
17 have an early stage of that condition.

18 It is also true that in the longitudinal studies
19 which document progression to Alzheimer's disease in some
20 proportion of patients that there is some proportion of
21 patients who don't progress to Alzheimer's disease. That
22 might possibly be an artifact of the fact that the follow-up
23 in those studies was not long enough. I suppose if you
24 follow long enough it is possible that all patients would
25 progress to Alzheimer's disease but, nonetheless, the

1 finding is that not all patients do progress. If that is
2 true, then it raises the possibility that maybe MCI isn't
3 early Alzheimer's disease but a separate clinical entity and
4 one that may be considered a risk factor for Alzheimer's
5 disease but not identical to Alzheimer's disease.

6 Another possibility is that, in fact, the symptom
7 cluster that we call MCI, in fact, is a clinical
8 manifestation of various and several different underlying
9 pathologies. If that is true, it raises the possibility
10 that before we would grant a claim for a drug to treat MCI
11 we might require sponsors to study MCI in the context of
12 several of these different pathologies. An analogous
13 situation would be the granting of a claim for a simple
14 analgesic where sponsors are required to study several
15 models of pain before they get a global analgesic claim.
16 That might be a particularly difficult thing to do in MCI
17 because is it not immediately obvious what those differing
18 underlying pathologies might be but that is a potential
19 approach.

20 As probably most of you know, the current
21 requirements for studies designed to establish effectiveness
22 of a treatment in Alzheimer's disease require that a drug be
23 shown to have an effect on a cognitive measure and on a
24 measure of global functioning. And, this makes sense
25 because all patients with Alzheimer's disease have cognitive

1 dysfunction and they all also have global dysfunction. But
2 most of the definitions of MCI that I described earlier
3 suggest that patients have very minimal cognitive
4 dysfunction and very little to no global dysfunction. So,
5 the sorts of outcomes that we ordinarily require for
6 Alzheimer's treatments might not apply for studies designed
7 to look at patients with MCI.

8 It is important, I think, to realize that even if
9 you decide that MCI is just early Alzheimer's disease the
10 question of what would appropriate outcomes be to study this
11 particular subset of those patients is critical, assuming
12 that if that is what you conclude sponsors are still
13 interested in studying it.

14 So, in summary, we are interested in your views on
15 a number of issues that we consider critical to the adequate
16 evaluation and potential approval of treatments for MCI.
17 Again just to sum up, specifically we are interested to know
18 if people believe that there is a specific set of diagnostic
19 criteria that reliably and reproducibly can identify
20 patients with MCI; whether or not these criteria simply
21 identify a subgroup of early Alzheimer's patients or whether
22 MCI is actually a fundamentally different disorder; or, as I
23 mentioned earlier, whether or not it is the clinical
24 manifestation of several different underlying pathologies.

25 We are also, as I say, are very interested in your

1 views on what studies ought to look like in patients with
2 MCI if they are done, and in particular what primary outcome
3 measures should be in these patients. Of course, we are
4 also interested in any other design elements of studies or
5 any other issues that you think are relevant to help us
6 grapple with this problem.

7 So with that sort of regulatory framework in which
8 we can, hopefully, fit the discussion, I will turn it back
9 to Dr. Kawas and I will thank you again for the work that
10 you have done so far and for the work you will do later
11 today, and I look forward to a fruitful and interesting
12 discussion. Thanks.

13 DR. KAWAS: I want to thank Dr. Katz and the FDA
14 for all the work that they have done so far, but this
15 committee's work is about to be started. So, now Dr. Ron
16 Petersen, from the Department of Neurology at Mayo Clinic.
17 I also want to point out to all the committee members that
18 in your beige folder you do have a copy of all the slides
19 that you will be seeing in case you need to look back.

20 Mild Cognitive Impairment: Unresolved Issues

21 DR. PETERSEN: Good morning.

22 [Slide]

23 I want to thank the FDA, Dr. Katz, Dr. Temple, Dr.
24 Mani, Sandy and Claudia for the invitation to come and speak
25 this morning. Sandy had to update one consultantship just

1 recently. Since that was submitted I also have been a
2 consultant to Elan American Home Products, for the record.

3 [Slide]

4 Since Dr. Katz very nicely outlined the problem
5 this morning, I am going to move very quickly. Fortunately,
6 all the information is in the handouts that Sandy has
7 provided. So, I am really going to scoot here and I am
8 going to hit all of these topics very briefly and, more, lay
9 the groundwork for subsequent discussions. We can certainly
10 come back to these in greater detail.

11 [Slide]

12 This is a slide that I use over and over again,
13 and I apologize, because it conceptualizes the concept, to
14 me, which Dr. Katz was talking about with regard to mild
15 cognitive impairment, MCI, being sort of a transitional
16 condition between normal aging, dementia -- say, Alzheimer's
17 disease. Note here the intentional overlap in diagnostic
18 criteria perhaps, and also here. In fact, people are
19 investigating this juncture, here. Some studies recently in
20 neurology, out of France, looked at this area. Some more
21 recent studies, out of Washington University, have looked at
22 this juncture. But that doesn't eliminate the fact that
23 this is still an in between transitional kind of condition.

24 [Slide]

25 Another way to look at this, if this is definite

1 Alzheimer's disease, pathologically confirmed, probable
2 Alzheimer's disease via the usual criteria that are in the
3 literature and have been used for approving drugs on the
4 market thus far, we put mild cognitive impairment right
5 after this inflection point in function. Cognition, normal
6 aging is moving along and starts a downward deflection.
7 This phase, prior to meeting the clinical criteria for
8 probable Alzheimer's disease, is what we have been referring
9 to as mild cognitive impairment.

10 [Slide]

11 Two of the questions that Dr. Katz has posed --
12 can MCI be defined in the clinical setting and are there
13 valid criteria for the diagnosis of MCI?

14 [Slide]

15 These are the criteria that we have generated in
16 our longitudinal studies of aging, in Rochester, Minnesota.
17 As you know, the Mayo Clinic provides the healthcare for the
18 local community and, after studying a group of aging
19 individuals, normal, mildly impaired, demented, over about
20 fifteen years, these criteria have evolved and we have used
21 these for longitudinal studies of aging.

22 The person should have a memory complaint,
23 preferably corroborated by somebody who knows the subject
24 well. Their general cognitive function, other non-memory
25 cognitive domains largely normal. Activities of daily

1 living are essentially preserved. But when you bring them
2 into the laboratory, into the office, and you measure their
3 memory function they are impaired for their age and their
4 education. So, it is a change in their function by their
5 memory complaint and it is objective documentation that, in
6 fact, they are performing at the bottom of their age and
7 education mates. Very importantly -- very importantly, they
8 are not demented. They do not meet clinical criteria for
9 dementia. That is why this group falls somewhat in between.

10 [Slide]

11 I won't spend a lot of time on this. The top two
12 panels refer to indices of general cognitive function --
13 Mini-Mental, upper left; Full Scale IQ, upper right. The
14 two bottom panels are indices of memory. The left is verbal
15 memory; the right is non-verbal memory. These our normal
16 controls in our community population. Here is how the MCI
17 people function. Note that statistically they are down a
18 bit and, yet, they are more like the normals than not except
19 with regard to memory. Memory function is down a great
20 deal. If you take very, very mild Alzheimer's, CDR 0.5,
21 they are different with respect to cognitive function,
22 general cognitive function, here. There is a difference
23 here. So, other cognitive domains are involved. Functional
24 impairment is now involved and their memory, again, looks
25 much like the Alzheimer's patients. The next grade of CDR 1

1 also shows the same relationship.

2 [Slide]

3 The next question, what outcome measures might be
4 appropriate to use in clinical drug trials?

5 [Slide]

6 As Dr. Katz indicated, many of the trials have
7 been looking at progression to clinically probable
8 Alzheimer's disease. In our longitudinal studies people
9 tend to progress at about 12 percent per year. Note, this
10 is 50 percent down here, not zero. So, after about 48
11 months about 48 percent of the group has progressed in
12 contrast to normal elderly individuals in the same
13 population who progress at 1-2 percent per year.

14 [Slide]

15 Do all of them progress? Well, we followed them
16 out about 6 years and there are probably about 160 people
17 who go into this survival curve. If you follow out about 6
18 years, 80 percent of them have converted. Will all of them
19 convert? I don't know. I think if we follow longer there
20 will be a greater conversion but probably not all. There
21 may be some in there that are misdiagnosed, if you will, but
22 do not meet the conversion.

23 [Slide]

24 FDA question number five, should clinical drug
25 trials in MCI incorporate any special features in their

1 design?

2 [Slide]

3 There are some features that do predict who is
4 more likely to progress more rapidly. There are features of
5 memory performance. In the ADCS trial, that Dr. Grundman is
6 going to talk about later this morning, there has been an
7 enrichment, if you will, in the memory criterion to enhance
8 for conversion over time. So, you can do that and there are
9 qualitative features of memory. It turns out apolipoprotein
10 E4 carrier status predicts more likely progression and there
11 are neuroimaging variables.

12 [Slide]

13 Here is survival data for E4 carriers versus non-
14 E4 carriers.

15 [Slide]

16 Here are some neuroimaging data with regard to
17 structural MR, volume of the hippocampus, entorhinal cortex,
18 functional measures, SPECT, PET, MR spectroscopy.

19 [Slide]

20 Here are survival curves for a fairly normal
21 looking hippocampal volume, a mild to moderate hippocampal
22 atrophy at the beginning of the study and more severe
23 hippocampal atrophy. So, this tracks into the primary
24 memory structure in the brain that is involved, and also the
25 earlier site of neuropathological involvement in Alzheimer's

1 disease.

2 [Slide]

3 Spectroscopy data -- I won't go into this now but
4 spectroscopy data show that, in fact, there is a difference
5 between mild cognitive impairment and normal controls, and a
6 further spectroscopy change between Alzheimer's disease and
7 mild cognitive impairment, again, leading to the idea that
8 this is progression.

9 [Slide]

10 Let me briefly hit on some of the issues that have
11 come up as to why there is variability in the literature,
12 why don't all the studies look alike. Well, there are
13 several factors that come into play. One has to do with
14 rating scales, and we will be talking about that later on
15 this morning.

16 If this is the clinical diagnostic continuum that
17 I have been talking about -- again, clinical diagnostic
18 criteria for these concepts, if you take the Clinical
19 Dementia Rating Scale now, CDR 0.5 is the closest but it is
20 not isomorphic. That is, CDR 0.5 does not equal MCI as we
21 have been talking about it. Most people with MCI do have a
22 CDR 0.5, but if you have a CDR 0.5 you can also be demented;
23 you can reach criteria for dementia. The recent study that
24 is coming out from Washington University shows that CDR 0.5
25 people down here have Alzheimer's disease in the brain. So,

1 a little further down the spectrum the Alzheimer's disease
2 continuum manifests itself.

3 Similarly with the Global Deterioration Scale,
4 and Steve Ferris is going to talk about this a little bit
5 later, GDS 2 and GDS 3, again, as we have defined it, they
6 don't map completely one to one onto mild cognitive
7 impairment criteria.

8 [Slide]

9 So if we look at our database and we say, okay,
10 how do people stack up, some of the boxes on the CDR. Our
11 mild cognitive impairment people who come out at about 1.07.
12 This is adding up the box scores and, again, we can talk
13 about this later. Normals are essentially zero, and the
14 very, very mild AD CDR 0.5 have about 2.5. So, there is
15 largely memory involved; maybe orientation.

16 With regard to the GDS, similarly they are not
17 quite 2; they are not quite 3. Where are they? They are
18 somewhere in between. The mean GDS of people with mild
19 cognitive impairment is about 2.5.

20 [Slide]

21 How can we be certain that we are not calling
22 people who are aging normally demented? How do we know that
23 these people are, in fact, pathologically involved with
24 regard to their cognitive function? I think it is a big
25 challenge. I think this is a problem and something that we

1 have to address.

2 Part of the problem is that when you say somebody
3 has a memory impairment -- with respect to what? Do you use
4 young normals as was done in AAMI criteria? Do you use a
5 change in performance? You document memory at one point of
6 time and you follow? That would be nice but we often do not
7 have the luxury of having longitudinal data. Do you use
8 age-appropriate normals? That is what we have chosen since
9 we have age and education appropriate normative data on our
10 community. Not everybody has that but people can claim that
11 even those norms are contaminated. That is, you have people
12 with incipient MCI or incipient AD in their normative data.
13 So, there is no perfect answer to this, and I think this is
14 a real challenge for the area of what is cognition in normal
15 aging.

16 [Slide]

17 Where do you get your subjects? That is another
18 source of variability in the literature. If you take people
19 who come to a referral clinic, the average dementia clinic,
20 Alzheimer's center and the like, most of the time by the
21 time somebody comes through the front door they are
22 demented. By the time they recognize the cognitive problem
23 and the family has recognized the cognitive problem, they
24 are demented.

25 If you go out and survey the community by

1 advertising you are likely to pick up very, very mild people
2 but you are also going to have to be concerned about the
3 "worried well," that is, people who are just overly
4 concerned about their memory function but, in fact, they are
5 doing quite well.

6 If you go to general practice clinics, that is a
7 good source of patients but then you have a threshold kind
8 of problem. How do you take people out of a primary clinic?
9 Do you wait for the doctor to call it? Do you wait for the
10 patient to call it? So, again, it is very, very important
11 to look at each study as to what is the source of the
12 patients -- not that they are good or bad but it can
13 influence how the patients are defined, what stage they are
14 at and how they progress.

15 [Slide]

16 Question number three was can MCI be distinguished
17 from Alzheimer's disease, on the one hand, and other forms
18 of dementia? Dr. Katz talked about the heterogeneity of the
19 concept.

20 [Slide]

21 What we have been talking about is so-called
22 amnesic form of MCI, that is, memory disorder and
23 everything else is relatively well preserved. Most of these
24 cases will go on to be Alzheimer's disease. All of them?
25 Probably not, but most of them.

1 Are there other forms of mild cognitive
2 impairment? You could have multiple cognitive domains down
3 a little bit. So, a little bit of memory; a little bit of
4 attention; a little bit of language naming problem but,
5 again, not sufficiently severe to constitute the diagnosis
6 of dementia. That still may be a prodrome for Alzheimer's
7 disease but it may also be a manifestation of aging --
8 again, getting to where do you draw that line kind of
9 question. So you can define it and some of the longitudinal
10 studies are using this as a definition for mild cognitive
11 impairment.

12 Finally, you could have another non-memory
13 cognitive domain, a single domain involved but it is not
14 memory. Frontotemporal dementia. It could be frontal
15 executive function, comporment, behavioral problems,
16 personality changes -- these could be the prodrome of
17 frontotemporal dementia. Maybe visual spatial impairment
18 could be the prodrome of Lewy body dementia; primary
19 progressive aphasia, language problem, etc. So, it is
20 incumbent upon all of us to clarify what we mean by mild
21 cognitive impairment.

22 [Slide]

23 There are certain semantic issues that come up in
24 this -- again, what is normal aging? As I said earlier, I
25 think this is absolutely a fundamental issue that we need to

1 address.

2 Is this Alzheimer's disease? Well, it certainly
3 is a prodromal stage for Alzheimer's disease but, by the
4 currently published clinical criteria, by definition these
5 people do not meet that. These people are not functionally
6 impaired and their other cognitive domains are largely
7 intact.

8 Is this a continuum? I think if we are talking
9 about the Alzheimer's disease spectrum and amnesic mild
10 cognitive impairment, I suspect that it is.

11 Will neuropathology answer the question? Tough
12 issue. Dr. Katz alluded to this and the fact that people
13 don't die generally when they are in the mild cognitive
14 impairment stage unless they die of heart failure, cancer or
15 something of that nature. There are relatively few
16 neuropathology studies. The one that is coming out this
17 week talks about people in the more severe mild cognitive
18 impairment, early AD CDR 0.5 stage.

19 We have done some autopsy data and in a sample of
20 about 10 individuals over 15 years who have died during this
21 stage, about 60 percent, 65 percent of the people will meet
22 criteria for very mild Alzheimer's disease, medial temporal
23 lobe involvement of tangles of plaques and diffuse amyloid,
24 a few neuritic plaques. Some of the people have tangle only
25 disease of the medial temporal lobe, hippocampus. Some

1 people have things like argyrophilic grain disease. All of
2 them have medial temporal lobe pathology, and with this is
3 sort of burgeoning Alzheimer's disease is a judgment call
4 but I suspect most of them are, but not all of them.

5 [Slide]

6 I think this is a clinically relevant concept.
7 That is, it is not a concept that you have difficulty
8 explaining to people, be they lay people or clinicians.
9 Clinicians say, yes, I know what you are talking about; I
10 have these people in my practice, I see them and I don't
11 know what to do with them. So, I think this is an entity
12 that is easily recognizable by clinicians and by the public.
13 However, it falls in the cracks. It is not currently
14 codified. It is not "is this Alzheimer's disease?" "Is
15 this normal?" "What is this?" So, that is a problem.

16 I think as more and more studies are being done
17 longitudinally and with the several clinical trials that are
18 available now, clinical criteria do exist and are fairly
19 reliable. It can be done on a multi-center basis. Mike is
20 going to talk about the ADCS study and 70-75 centers are
21 involved in this using the same set of criteria, a spin-off
22 of what I said earlier, and it appears to be doable.

23 The outcome measures, if you use the amnesic form
24 of the diagnosis of MCI, appear to be fairly reasonable,
25 that is, clinically probable Alzheimer's disease, and

1 neuropathologic confirmation of most of these cases. So, I
2 think there is a regular progression if you refine the
3 criteria.

4 Importantly, and this is where the distinction
5 from AAMI, age-associated memory impairment, AACD, age-
6 associated cognitive decline -- these people are not normal.
7 This is felt to be a pathologic condition that is an
8 incipient or prodromal stage but they don't meet criteria
9 for dementia. So, it is a bind in that sense. They are not
10 functionally impaired in their other cognitive domains and,
11 just from a clinical standpoint, when you see these people
12 in the office you would have a great deal of difficulty
13 saying that this person is demented. These people by and
14 large are memory impaired but otherwise quite functional,
15 living independently in the community.

16 So, are they are therapeutic target? At least
17 from an investigational standpoint they would be and, of
18 course, if in fact there is an agent that is able to slow
19 down this progression or even treat the symptoms at this
20 stage that would have a huge impact on the individuals,
21 their families and the healthcare system as a whole. So,
22 from that standpoint I think it remains to be seen but it
23 may very well be that this is a therapeutic target.

24 [Slide]

25 I think the edges here are fuzzy but, in fact,

1 there is a position for some transitional state between
2 normal aging and very early Alzheimer's disease, and I think
3 the term mild cognitive impairment sort of fills that niche
4 right now. It needs to be refined with regard to criteria
5 and outcome but I think it does, in fact, serve a useful
6 purpose.

7 [Slide]

8 I just should acknowledge these. As you know,
9 these large multi-center efforts are not the efforts of a
10 single individual. We have a huge staff at our Alzheimer's
11 disease center, both in Rochester and Jacksonville. Let me
12 stop there. Thank you very much.

13 DR. KAWAS: Thank you, Dr. Peterson. I don't know
14 how but we are still miraculously on time and the floor is
15 now open for questions.

16 DR. PENIX: Dr. Petersen, when you say in your
17 conclusions about mild cognitive impairment that they are
18 not normal, I presume you mean that there is some
19 pathological basis for them not being normal. For that
20 percentage of patients who have not developed Alzheimer's
21 disease, what is that that abnormality do you think?

22 DR. PETERSEN: When I say that they are not normal
23 I am referring to them clinically, that their memory
24 function is really not normal for their age and education.
25 Again, if someone were to die at that point in time, I think

1 virtually all of them have some pathology of the medial
2 temporal lobe -- so the hippocampus, entorhinal cortex.
3 Usually it is tangles; some plaques; early Alzheimer's
4 disease. It could be other pathology. It could be
5 hippocampal sclerosis, whatever that is -- some pathology of
6 the medial temporal lobe. Although I think if one were to
7 do a large-scale study on this the vast majority would have
8 Alzheimer type changes, and I think what you see in the
9 cortex in these individuals is diffuse amyloid with a few
10 neuritic plaques giving you the impression, looking under
11 the microscope, that had this person lived another two,
12 three, five years their cerebral cortex would have been full
13 of neuritic plaques.

14 DR. KAWAS: Dr. Katz?

15 DR. KATZ: Could you detail a little more the
16 substantive distinction between these patients, in your
17 view, and patients with, let's say, AAMI which is considered
18 sort of a normal phenomenon. Those patients have an
19 isolated memory deficit and in your definition of MCI, it
20 seems to me, it also is basically isolated memory deficit.
21 So, is it the nature of the memory deficit that's different?
22 The severity?

23 DR. PETERSEN: The difference between this concept
24 and AAMI is with the reference group. On one of the slides
25 I talked about how do you reference people. The criteria

1 for AAMI reference the memory impairment to performance of
2 young adults, so people in their 20s and 30s. I think the
3 AAMI criteria were one standard deviation below young
4 normals, young adults -- say, a 30-year old's memory
5 performance.

6 We took those criteria and applied them to our
7 normal population who have been independently characterized
8 as being normal in our normal aging cohort. Depending upon
9 which memory test you use, you can, in fact, include up to
10 90 percent of the normal population under the rubric of
11 AAMI. That is, if you use one of the more difficult
12 challenging memory tests, like Auditory Verbal Learning
13 Test, a 15-word list that you learn over 5 trials and you
14 recall it half an hour later -- a very demanding test. Most
15 older individuals, if you use, say, the delayed recall
16 component of that measure, most individuals who are aging
17 normally will fall one standard deviation below young
18 normals. That is where the reference group issue becomes
19 very important.

20 I am not saying that age appropriate, education
21 appropriate norms are the best but I think they are an
22 improvement on the young normals, but that remains an issue.
23 But it is largely the reference group that is the
24 difference.

25 DR. VAN BELLE: As to the reference group issue,

1 are there other subgroups that you are aware of? Say,
2 gender, socioeconomics, race? Are those associated at all
3 with mild cognitive impairment? If so, how would you use
4 that to distinguish people in these various subgroups?

5 DR. PETERSEN: I think that is a good question,
6 are there other factors, other variables that come into
7 play. I can only extrapolate from our normative data and,
8 as you know, they are relatively homogeneous, certainly with
9 regard to ethnicity, racial background in the upper Midwest.
10 So, looking at our normative data and looking at gender
11 issues and all of the other ones that we can look at in our
12 population, it was only age and education that turned out to
13 be the ones that we had to correct for when we did our
14 comparisons. But I suspect you are right. I mean, I don't
15 think you can easily translate, say, criteria that we use to
16 another population. I think conceptually you can but where
17 you put, say, cut-off scores and things like that would be
18 more challenging.

19 DR. FERRIS: Two specific comments or issues that
20 maybe you could address further, you referred to AACD which
21 really came out of a consensus group in Europe, and I think
22 you are quite right about the distinction with respect to
23 what your reference group is. From that standpoint, AACD
24 uses as a reference group normative aging data and,
25 therefore, it is very MCI-like in its conceptualization, and

1 that seems to be borne out by the recent Richie data where
2 there was a very high rate of conversion in the AACD group,
3 which is not consistent with AAMI or ARCD which is a
4 normative aging cognitive decline as distinct from a
5 disease. So, you know, I think that ought to be considered.

6 The second question is perhaps you could elaborate
7 a little more on why you focus on the notion of the isolated
8 memory impairment. The logic of that is not consistent with
9 the notion that normative aging changes include certain
10 domains other than memory, and certainly early Alzheimer's
11 disease includes domains other than memory and memory
12 impairment is almost universal in both of those ends of the
13 spectrum. So, if MCI is, in fact, in between, which I think
14 is right on target, why would you want to rigorously
15 restrict the domains of in between impairment to just
16 memory? In fact, I think a number of data sets suggest
17 otherwise.

18 DR. PETERSEN: Right, good questions. Let me try
19 the second one first. I think the issue of why we focused
20 on memory grew out of our clinical experience and the fact
21 that most people who go on to develop Alzheimer's disease
22 will have incipient, progressive forgetfulness as the
23 hallmark and then other cognitive domains become involved.
24 Also, from a pathologic standpoint, the earliest involvement
25 again of pathologic markers are in the medial temporal

1 regions. Imaging studies show that the earliest markers of
2 Alzheimer's disease, even prior to diagnosis, again reflect
3 medial temporal, or hippocampal atrophy, entorhinal cortex,
4 etc. All these point to memory as being the hallmark.

5 But you are quite right. That does not mean that
6 that is the only prodromal phase or presentation of
7 Alzheimer's disease. There are many cases in the
8 literature. Everybody's dementia center has a variety of
9 cases with other presentations. So, this does not imply
10 that this is the only exclusive prodromal stage of
11 Alzheimer's disease but I think it is the most common.
12 Since the current criteria for Alzheimer's disease, the
13 NINCDS/ADRDA criteria say you have to have memory plus -- so
14 it is really trying to capture what is happening most
15 frequently. But there are other presentations and that is
16 why the other slide included multiple cognitive domains down
17 a little bit which most closely resembles the AACD notion.
18 AACD refers to cognitive domains down a little bit, say, one
19 standard deviation -- not just memory but it can be others.
20 The recent paper by Richie and colleagues indicated that
21 this may, in fact, be a prodromal condition.

22 I won't take a lot of time to critique that paper
23 but the way the criteria were applied in that paper for mild
24 cognitive impairment is not consistent with what we have
25 been talking about. So, it is not a direct comparison but,

1 nevertheless, the concept is that there can be other
2 presentations of incipient Alzheimer's disease or prodromal
3 state, and I think that is appropriate.

4 DR. KAWAS: Dr. Katz and then Dr. Temple.

5 DR. KATZ: You have already sort of said this, I
6 think, but you might be able to address the question
7 explicitly. If 80 percent of these patients go on to frank
8 Alzheimer's disease over the course of 6 years in your
9 cohort, and we have been talking about it being a prodrome
10 for Alzheimer's disease, it may be just semantics but for
11 our purposes I believe semantics are very important, would
12 you say this is early Alzheimer's disease that just hasn't
13 really met the criteria that currently are established for
14 that diagnosis?

15 DR. PETERSEN: I think if you turn the question a
16 bit and say what will be the outcome of most of these people
17 with the amnesic MCI, again, the vast majority, 80-plus
18 percent, will probably go on to be Alzheimer's disease. Is
19 this early Alzheimer's disease? It is a semantic issue I
20 guess. I mean, where do you draw the line? By definition,
21 no because one of the criteria for MCI is not demented. So,
22 they are mutually exclusive in that sense.

23 But your question is well taken, is this just a
24 semantic issue? It is to a certain extent but it is not a
25 trivial one. For your purposes or from the practicing

1 clinician standpoint, these people do not look demented.
2 So, I think if we just say, "ah, this is just early
3 Alzheimer's disease; that is what it is," I think we are
4 doing them a disservice. There still is a social stigma to
5 have that label and it affects a lot of other aspects of
6 their lives. So, it may be a more responsible position for
7 clinicians at least to say you have a condition that
8 research indicates -- still evolving research but research
9 indicates that you are at a higher risk of becoming
10 demented, developing Alzheimer's disease in the next few
11 years, meaning that in 4 years you may have a 40-50 percent
12 chance; 40-50 percent you won't be there but this allows
13 people to do planning, counseling, whatever they want to do
14 for this. But it is different from saying, no, research
15 shows at this point in time you have Alzheimer's disease. I
16 think that is an overstatement from a clinical standpoint.

17 Am I dodging your question? Perhaps. Is this
18 early Alzheimer's disease? Well, most people are going to
19 go on. If you use the amnestic definition most people are
20 going to go on to fulfill the criteria for Alzheimer's.

21 DR. KAWAS: Dr. Temple?

22 DR. TEMPLE: The question about endpoints of
23 studies, which I think is somewhat related to the previous
24 discussion, you suggested that there are two that might be
25 reasonable. Dr. Katz also did. One is actual symptomatic

1 improvement -- resolution or improvement of their complaint
2 about memory problems. The other would be time to
3 progression to Alzheimer's disease.

4 It is the second I want to ask about. If you put
5 normal people on diuretics you probably would see less
6 hypertension after a period of time because you have treated
7 the hypertension that was going to develop before it arose,
8 and you could do that but there would be a significant
9 question about whether you have done anybody any good.
10 Similarly, if you delay the time to the official diagnosis
11 of Alzheimer's disease but haven't shown any improvement in
12 a symptom that anybody can recognize, and haven't also shown
13 that when you take the drug away they are less likely to
14 have Alzheimer's disease, that is, a genuine delay in
15 progression, have you accomplished anything?

16 DR. PETERSEN: I think that from a public health
17 standpoint and from an individual patient family standpoint
18 you probably have. That is, I think while these people are
19 quite functional, they are not normal. So, if you can
20 improve their function that would be great. If you can
21 improve their memory function that would be great, getting
22 them back toward a more normal condition. But even if you
23 held them at that level such that what would have been a
24 conversion rate of 48 percent in 4 months is now 24 percent
25 in 4 months I think that has a significant impact for them

1 personally, for the family and for the whole healthcare
2 system.

3 So, in much the same way of Alzheimer's disease
4 drugs, I think you can think about them in the same fashion
5 and I think that symptomatic improvement would be
6 significant. Of course, if drugs become available that do
7 have an impact on the underlying pathophysiology so that if
8 you have a drug that prevents the deposition of plaques, or
9 whatever, then you are dealing with an even more significant
10 situation, if you can stop it at that point and keep them
11 there. So, I think the same thinking applies to MCI as it
12 does to Alzheimer's disease.

13 DR. TEMPLE: But in the latter case, where you
14 have actually delayed progression and you can see that in
15 people who are not on the drug, you are right, that is easy.
16 That is a clear boon. I am a little worried that the
17 implication of delayed time to Alzheimer's is overstated.
18 That is, it is misleading. It may be, as Russ just
19 whispered, that all you are really showing is that you are
20 improving symptoms.

21 DR. PETERSEN: Right.

22 DR. TEMPLE: And that you are setting a target
23 level to which you held them. But I guess I would ask
24 whether if you are not changing the fundamental progress of
25 the disease the focus shouldn't be more on the degree and

1 documentation of symptomatic improvement in the course of
2 the treatment because that is the real benefit to the people
3 if you haven't changed the underlying pathology. But this
4 may be more of a semantic problem too. I am sure this is
5 going to come up a lot.

6 DR. KAWAS: Dr. Weiner and Dr. DeKosky and then
7 Dr. Duara and then me, if you haven't asked my question by
8 then, and then we will move on to the next speaker.

9 DR. WEINER: I would like to discuss a bit again
10 this 80 percent that go on to Alzheimer's and also the
11 definition and get some insight from you in terms of
12 pathology, in terms of imaging and how many patients have
13 really been studied, and what we know.

14 Clearly, the definition of Alzheimer's in terms of
15 dementia is purely a clinical definition, not an underlying
16 definition of what is going on in the brain. How effective
17 or how available is any testing, with it is imaging, spinal
18 fluid analysis or any other analysis, in this group to
19 identify that they, indeed, have the process that is going
20 to lead to Alzheimer's or that there is an underlying
21 pathology there? How big have those studies been?

22 DR. PETERSEN: We and others, many in this room,
23 have done some of these longitudinal studies but I can speak
24 about our work on imaging. We have done hippocampal volumes
25 cross-sectionally and longitudinally in normal elderly

1 subjects. This is the work of my colleague Cliff Jack, and
2 he has studied normal elderly in the quantity of 200 people
3 in the community, and followed them cross-sectionally and
4 many of them longitudinally. The MCI people -- I forget the
5 N in the paper but it is probably in the 90-ish range of
6 people who have been imaged with that. Of course, we have
7 many, many Alzheimer's disease patients. So, I think the
8 data from that standpoint are fairly reliable, and they are
9 consistent with what other groups have obtained. You can
10 argue that it is the entorhinal cortex, or the hippocampus
11 or this or that, but the point is that these are relevant
12 structures that are being followed.

13 So, I think the strongest biological data, if you
14 will, biomarker data come from the imaging, the structural
15 imaging. I presented some spectroscopy data, small numbers,
16 20, 30 per group and you don't go to the bank with that.
17 That and SPECT have been looked at as well. There are some
18 papers emerging now on biomarkers, CSF biomarkers, and,
19 again, smallish numbers but some of the papers indicate
20 that, in fact, the people who are more likely to progress
21 have high CSF tau and low a-beta-1 to 42. So, again,
22 consistent with an Alzheimer's kind of picture but, again,
23 the numbers are small and it really is a big deal to do
24 these longitudinal studies.

25 DR. WEINER: I understand. In those studies, what

1 percentage have those abnormalities? You said 80 percent of
2 people go on to Alzheimer's.

3 DR. PETERSEN: Right.

4 DR. WEINER: What percentage of the MCI patients
5 had any of these abnormalities by structure?

6 DR. PETERSEN: By structure, I don't have a number
7 off the top of my head but many do. The survival curves
8 that I presented on the degree of atrophy at the time of
9 diagnosis of MCI predicting progression are based on 90 or
10 so individuals. So, in fact, I would say -- again, it is
11 off the top of my head but I would say that 70, 75 percent
12 of the people at least have atrophic hippocampi at the time
13 of diagnosis of mild cognitive impairment. That is a ball
14 park but I think it is about right.

15 DR. FERRIS: Could I just throw in some additional
16 data on that, just for one second?

17 DR. KAWAS: I have to tell you, Dr. Petersen, you
18 have a stimulating presentation because there is not a
19 single person around this table who doesn't want to throw in
20 something. Okay, you have twenty seconds.

21 DR. FERRIS: Twenty seconds to second what Ron
22 said about neuroimaging. From the population at NYU, the
23 work of Maury De Leon's imaging group, 80 percent of people
24 with MCI cross-sectionally have hippocampal atrophy, and it
25 predicts with 90 percent accuracy conversion to Alzheimer's.

1 DR. DEKOSKY: I just have a comment for Dr.
2 Temple. If I understood the comment correctly, if you were
3 to symptomatically, and not from a disease progression
4 mechanistic halting, stop further movement of someone with
5 an amnesic disorder to Alzheimer's disease, considering the
6 fact that the majority of the patients to whom this will
7 apply are of the age of 75 or 80, with the increasing
8 problems of other kinds of domains -- visual, spatial
9 orientation, effects on driving and so forth, and their
10 functional declines, people in that late age group held off
11 for a couple of years represents a significant family
12 advantage and also represents a significant fiscal advantage
13 to the system. To be very pragmatic, until there are more
14 effective medications that stop plaques and tangles,
15 anything that will suppress the evolution of more symptoms
16 that makes people more dependent, who are at risk and cost
17 more to the system, is probably a benefit if you can show
18 that, in fact, that symptomatic withholding of a worsened
19 clinical cognitive diagnosis is true.

20 DR. TEMPLE: I think it is as much a matter of
21 focus as anything else. I mean, if a person didn't have
22 another complaint at all, why would you institute treatment
23 before they had it? I mean, maybe if a drug were extremely
24 safe you might consider that, but why would you do that
25 unless you were actually preventing the underlying disease

1 where everyone would agree that it would be worth treating?
2 But suppose you are not preventing the underlying disease,
3 merely treating a symptom before it arose. My example with
4 hypertension, I suppose you could make an argument that you
5 would treat a blood pressure before it arose, but if you
6 haven't changed the underlying disease so that it wasn't
7 there when you take the drug away, I think people would
8 wonder whether that would make sense.

9 DR. DEKOSKY: I think most people who have watched
10 family members go from MCI into the disease would say, "sure
11 it makes sense. I don't care how you stop anybody from
12 getting worse. If you have a way to stop it, go ahead and
13 stop it." Our goal, everybody's goal is to find something
14 that actually works on the fundamental disease mechanism but
15 the pragmatic act of slowing down entry into the observable
16 and functional impairment of the disease I think is a
17 worthwhile goal. I recognize the difference. I used to
18 think that hypertension was a perfect analogy. I am not so
19 sure anymore that that actually works with the increasing
20 amounts of data that suggest that most of these cases in
21 fact have AD, and I have some data that I will show in a
22 minute.

23 DR. DUARA: This is in reference to Dr. Katz's
24 question about are most of these patients actually in an
25 early stage of Alzheimer's disease, the cases that you have

1 defined here. I guess my question is would you agree that
2 your criteria, as you have designed them, are really based
3 on early AD and, therefore, it is sort of a circular
4 argument. They are earlier AD because that is the way you
5 have designed the criteria.

6 Now, if you used more broad criteria for MCI,
7 which is more like the AACD criteria, you may find that it
8 is a much more heterogenous disease. Would you agree with
9 that?

10 DR. PETERSEN: I do agree with that. If you
11 broaden the clinical characterization of your criteria for
12 prodromal, or whatever, you are going to get likely
13 progression. That is what that one slide was meant to
14 indicate. Again, if you take people who are down in a
15 another cognitive domain, like language, they may go on to
16 have primary progressive aphasia with a tauopathy
17 underlying that as the neuropathologic marker. So, I think
18 that is right.

19 We clearly have focused on prodromal Alzheimer's
20 disease and, therefore the memory and therefore the criteria
21 have been designed in that fashion. That is right.

22 DR. KAWAS: Dr. Grundman and Dr. Reisberg, sixty
23 seconds each and the we are going to move on.

24 DR. GRUNDMAN: I was just going to make the point
25 that I think in the Mayo Clinic -- getting back to the

1 question about hippocampal atrophy, the MCI patients were
2 about one standard deviation below the norms and the
3 Alzheimer patients were about two standard deviations below
4 the norm, and we find very similar data in our clinical
5 trial that we are doing now.

6 DR. REISBERG: Just briefly in response to what
7 Dr. Temple and Dr. Katz were saying, there are certain
8 symptoms which actually peak in the MCI stage. So, for
9 example, the magnitude of complaints of cognitive impairment
10 actually, and very interestingly, peak in that stage. So,
11 the patients certainly feel, before denial sets in, that
12 their memory is worse at this point. Also very
13 interestingly, certain behavioral symptoms, certain kinds of
14 anxieties, various anxieties, also occur in, first of all,
15 40 percent of these patients but also seem to peak in
16 occurrence at this point in the evolution of the condition.

17 DR. KAWAS: Actually, I would like to ask a
18 question of Dr. Petersen, and it has to do primarily with
19 the issue of defining this entity out in the clinical
20 setting. In particular, if this is such a readily
21 definable, criteria-driven entity, how can we get subjects
22 or patients from different sources? We have such a
23 different outcome.

24 The second question is in the clinical setting
25 what instruments would you recommend that the clinician be

1 using to identify these individuals? Would it be the four
2 that you showed us and the ones that we use in the research
3 environment, or what are your thoughts on that?

4 DR. PETERSEN: That actually is a very important
5 issue and a difficult one because while I think it is a
6 readily identifiable condition, that is, there are a fair
7 number of people who fall into this, I am not necessarily
8 convinced that it can be identified in a quick and dirty
9 fashion. That is, you have people come into the office and
10 you do a five-minute screen and you get the diagnosis or see
11 whether people meet the criteria. I think it is more
12 involved than that. Not that this is the gold standard by
13 any means but, for example, in the clinical trial sponsored
14 by NIA, for the not-dementia criterion we are using the
15 Mini-Mental State performance above 24. Now, that doesn't
16 guarantee it but it gives you a rough index of what people
17 are doing in a general cognitive sense. Then, we are using
18 a memory tool, paragraph recall, to guarantee that their
19 memory function -- delayed recall of that paragraph, is
20 below a certain point. Again, that is not the end-all, be-
21 all but I think it takes something like that. I don't think
22 it can be done quickly in the office setting.

23 DR. KAWAS: Thank you. Our next speaker is Dr.
24 Steven DeKosky, who is from the University of Pittsburgh,
25 Alzheimer's Disease Research Center.

1 late life cognitive disorders because, in fact, that is all
2 it means. I think it can be a useful concept and perhaps a
3 useful categorization if we carefully define it but I would
4 actually vote that we put together better names for
5 specifying that would allow physicians to more easily make a
6 diagnosis. We term it a risk state for the definition of
7 development of dementia of the Alzheimer type. The question
8 for us, as is clear from Dr. Petersen's data, is exactly how
9 high is the risk? Is it extraordinarily and incredibly high
10 or is it just moderately high?

11 [Slide]

12 We use two definitions of MCI at University of
13 Pittsburgh and it is based on our clinical experience in the
14 Alzheimer Center. You have heard these described briefly
15 already. One of them is what we call MCI amnestic, and this
16 is the MCI that we generally have been talking about here.
17 These are people who have an isolated amnestic disorder.
18 Most of them, but not all, have a CDR of 0.5 and this is
19 what in my clinic is referred to, with great respect, as the
20 Morrison or Petersen definitions, that is, isolated amnestic
21 disorder.

22 The reason we came to this division is because we
23 had a history, since this NIA funded center has been in
24 existence since 1985, of lots of other people who would come
25 in with less severe, non-specific cognitive complaints than

1 just memory who were followed over time and who progressed,
2 and we developed the extraordinarily specific identification
3 of MCI other. We defined this as deficits in two primary
4 areas of cognition that were less than 1.5 standard
5 deviations below the age and education corrected means, and
6 this has proved fairly helpful to us.

7 [Slide]

8 I asked my statisticians to give us the outcomes
9 for these cases over the time that we have been recording
10 these cases at Pittsburgh and, I must admit, I got this
11 slide last night and I was a bit surprised.

12 The first thing to comment on is that if you look
13 at the purple line, the purple line is the data from our
14 memory disorders clinic from the MCI amnestics. So, this is
15 comparable to most of the rest of the cases we have been
16 discussing and at 6 years we are down to about 85 percent;
17 at 5 years we are right around 80 percent, which is actually
18 a little faster than I thought it would be.

19 The interesting thing for us was that if you look
20 at the MCI cases in multiple cognitive domains, these are
21 people who do not meet criteria for Alzheimer's disease
22 because they do not have sufficient impairment in two
23 domains but they had two domains that were down. The line
24 shifts slightly, by the way. If you move it up to one
25 standard deviation as opposed to 1.5 they don't follow a

1 terribly dissimilar course, which surprised us. I actually
2 expected that this would splay out a little bit more. But
3 you do see that they splay out and at 5 years they are right
4 around 50 percent for conversion. These are the data for us
5 for time to their diagnosis of dementia.

6 [Slide]

7 The other comment I wanted to make had to do with
8 one of the things that we all presumed underlies this, and
9 that has to do with the cholinergic loss in Alzheimer's
10 disease. The ChAT data are fairly variable in a lot of
11 studies and all of you know that the early basis for the
12 cholinergic deficit as being one of the major causes of the
13 cognitive impairment stems from the studies in the 70s and
14 early 80s in which patients who had died came to autopsy and
15 the cholinergic deficit was discovered.

16 Three papers that have been published and some
17 data that I will show you briefly suggest that if you look
18 at people earlier on they don't have the same mass of loss
19 of cholinergic function. The study from Mount Sinai, from
20 Ken Davis' group, showed no loss of ChAT activity in
21 cortical regions in MCI as defined by a postmortem CDR in
22 some patients as well as in mild AD, and actually didn't
23 show a cholinergic drop in the cortex, that is, as defined
24 by ChAT activity in the cortex, until patients had severe
25 disease.

1 Tiraboschi -- the group from San Diego -- just
2 published a study last year showing similar changes confined
3 to the frontal lobe, also with postmortem CDRs, the
4 methodology for which everyone can always debate.

5 This actually was done at Atlanta by Alan Levey
6 and his colleagues, looking at quantitation of the number of
7 cholinergic basal forebrain cells in the brains of people
8 with AD with MCI from the religious order study, the Chicago
9 study of nuns and priests, and I will show you some
10 additional data on that in a moment, and showed, somewhat
11 unexpectedly, that they did not have all that much of a loss
12 of cholinergic neurons in the basal forebrain in MCI. So,
13 the early symptoms of AD may not be caused by cholinergic
14 enzyme deficits, that is, an absolute loss of the synthetic
15 enzyme although cholinergic dysfunction itself is still
16 present.

17 I think this is important from the standpoint, for
18 example, of the issues that Dr. Temple raised about if you
19 find something that actually stops the disorder or is in
20 some way an atrophic factor, how much brain tissue have you
21 got left and what are the tools with which the brain has to
22 repair itself and maintain cognitive function?

23 [Slide]

24 The religious order study is the study from which
25 the Levey trial was done. These are 900 nuns and priests

1 from the Chicago area who have been followed. This is not
2 David Snowden's study. Although we call this the ROS we
3 think it should be called the TONS for the other nun study.
4 But this particular group of nuns and priests undergoes
5 detailed neurological and neuropsychological and medical
6 examinations every year, and they are categorized to normal
7 MCI or Alzheimer's disease annually. They have neuropathic
8 evaluation after death and we did the cholinergic enzyme
9 assays.

10 [Slide]

11 This is a fairly old cohort. These are the
12 baseline characteristics. The living patients range now
13 from their late 70s up to their mid 80s.

14 [Slide]

15 The three groups were in overlap. This is not
16 exactly the same MCI definition as these are the data from
17 my center or the data that Dr. Petersen has shown, but their
18 normal cases are people who go through an extensive battery
19 of tests and are regarded to be well within the normal
20 range. Their mild cognitive impairment patients have some
21 impairment as defined by a Z-score of decline from the norms
22 of the group, but then a neurologist sees them and decides
23 they are not demented. It would be the equivalent of
24 someone looking at one of our MCI amnestics and saying, yes,
25 there is a memory loss but they don't meet criteria because

1 they don't have sufficient abnormalities in two domains.
2 Then, the AD cases use the standard NINCDS/ADRDA criteria.

3 [Slide]

4 So, we looked at ChAT in the autopsies of these
5 cases and found that, indeed, we did not see a deficit in
6 choline acetyltransferase activity. Our Ns are different.
7 That is, we have more cases now. These cases of AD are
8 relatively mild. They died with a Mini-Mental average of
9 about 16, which is relatively mild.

10 [Slide]

11 This is the anterior cingulate data from these
12 cases, again showing no significant changes across the
13 groups.

14 [Slide]

15 This is inferior parietal lobe, again showing no
16 differences but what we took was a dozen age and sex matched
17 cases from the University of Pittsburgh's brain bank. These
18 are the typical cases on which most of our work has been
19 based I think over the last 15 or 20 years. They are cases
20 we followed for five or seven years. They go into a nursing
21 home. We touch base with them by phone. They are committed
22 to autopsy. They come back to be autopsied and our cases
23 come back with the expected loss of 50 percent of ChAT
24 activity in this region of brain.

25 The Levey data suggested that the cells are still

1 there but now this is the fourth paper that suggests that if
2 you catch these patients earlier in the course they do not
3 have the massive loss of the synthetic enzyme we thought
4 then did.

5 [Slide]

6 One interesting finding, since we are obviously
7 interested in what the structural memory change is, in fact
8 there is a significant increase in ChAT activity in the
9 hippocampus which we believe is sprouting of the cholinergic
10 system related to the denervation by the entorhinal cortex
11 because those laminar-2 projections are, in fact, the first
12 places in the brain, we think, where neurofibrilla tangles
13 occur.

14 [Slide]

15 In Ken Davis' study, he looked at his cases that
16 had the postmortem CDR of 0.5 -- now we are moving to the
17 other transition stage that Ron discussed. The first was
18 what happens if you identify people as MCI, how do they move
19 to Alzheimer's disease. In this particular case, when Davis
20 looked at his postmortem CDRs, about 60 percent of these
21 cases would have met criteria for Alzheimer's disease at
22 autopsy. In our study of the cases, for which I showed you
23 the ChAT data, again about 60 percent of these cases --
24 these are defined by disease scores -- also had evidence of
25 AD. There is a bit of a paradox here. All of our cases

1 would get a diagnosis of possible AD under CERAD criteria.
2 Again, we are a victim of our definitions. To have a CERAD
3 definition of definite AD by autopsy you must have evidence
4 of dementia in life. So, we have a logical contradiction
5 here. We cannot say these patients had dementia in life;
6 they are the MCI cases. So, if they had enough plaques to
7 make a diagnosis by CERAD criteria of dementia the highest
8 they can get is a possible AD diagnosis. They would have to
9 have had evidence of dementia in life and those path changes
10 to get definite AD. But it is clear that a similar number
11 of cases, similar to the number that Ron discussed, look
12 like when they die at this relatively early stage they have
13 already met or would have met the path criteria, and I have
14 no doubt that cognitive reserve and the presence of vascular
15 disease or strokes may have something to do with who
16 manifests first, although these cases did not have strokes.

17 [Slide]

18 Let me turn last to the issue of can we define MCI
19 clearly in a clinical setting. I think you are getting the
20 message now, and Ron's last two questions also addressed
21 that. It requires a careful examination and
22 neuropsychological testing and/or a reliable informant. One
23 of the issues about the CDR is if you don't have a good
24 informant you are not going to get reliable data, and that
25 is still an issue. It is one of the reasons we think CDR is

1 variable. In fact, it is one of the reasons I was noticing
2 in Ron's data that he has ADs with a CDR of 0.5 and ADs with
3 a CDR of 1.0. It may be that that is because of accurate
4 observation of the patients, but it may also be because the
5 proxies or the informants also have a significant input into
6 the scoring.

7 Are there valid criteria? Well, I believe there
8 are reasonable criteria for amnesic MCI. Those are fairly
9 clear in a specialty clinic and that has predictive validity
10 that we have discussed. There is still uncertainty about
11 the underlying pathology although most of it appears to be
12 those cases who lose hippocampal function and structure
13 first as opposed to those cases who are dropping in a couple
14 of other areas, and it is not unreasonable despite the fact
15 that we know that the path starts in the hippocampus to have
16 people go down in other domains first and then eventually
17 have the hippocampus join them. Hippocampal atrophy, as you
18 have heard, is the best structural predictor.

19 [Slide]

20 Can we distinguish MCI from other causes of
21 dementia? Well, neuropsychological definition requires two
22 impaired areas of cognition and that is still the major
23 difference between MCI amnesic, just the memory loss, and
24 Alzheimer's disease by our standardized criterion. That is
25 it; it is the second domain. When you fall in the second

1 domain you have reached an AD diagnosis. The difference may
2 be quantitative or qualitative. That is the point that Dr.
3 Katz has raised, and there is not much we can do about that.

4 Amnestic MCI though can't be differentiated from
5 hippocampal sclerosis. We have a number of cases who have
6 presented with amnestic MCI, have come to autopsy and they
7 have a selective fibrotic change, a neuropathological loss
8 of cells in the hippocampus. This is a very, very rare
9 condition. And, some of our AD cases also have hippocampal
10 sclerosis. It is one of the studies under examination by
11 the ADCS. But this is one other kind of disorder that you
12 could say could mimic it.

13 [Slide]

14 Finally, should clinical trials incorporate any
15 special features in their design? One of the issues of
16 great interest would be a comparison of generalized MCI,
17 that is, something defined by losses which aren't the two
18 standard deviation losses but losses that are below that
19 expected for age and education versus amnestic, and what is
20 the effect on these cases because they probably represent a
21 significant number of cases out there. We are going to have
22 to find a way to make a diagnosis in the absence of an
23 informant because although in a specialty clinic like ours
24 we are blessed with concerned proxies who will come in and
25 give us information about change, out in the real world in

1 the trenches, as Dr. Ganguli will discuss, we don't always
2 have that reliable informant. As we do the prevention
3 studies in late life, beginning with people who are 70 or 80
4 as in some of the prevention trials now ongoing where after
5 five years the person and their proxy may be in their mid-
6 80s, the reliability of the proxies shifts and the proxies
7 give us an external view of what the patient is doing is not
8 going to be reliable when we make the diagnosis.

9 We absolutely will need to continue to look for
10 biomarkers, and that would include hippocampal atrophy or
11 perhaps other diffuse atrophy, such as the studies by Nick
12 Fox's group, other biomarkers that might be helpful that
13 would prevent us from having to say to the general clinician
14 you are going to have to do an intense neurocognitive
15 evaluation to be able to identify these patients early.
16 This is generally something that they don't want to do. If
17 they don't have time to do a Mini-Mental State exam they are
18 not going to want to do some of these other isolated studies
19 that we want done. So, I believe the disorder is unlikely
20 to be diagnosed quickly in a primary care setting using the
21 current techniques that we have.

22 [Slide]

23 Finally, for outcomes improvement in memory
24 function, I agree, is a perfectly reasonable thing to go
25 after. I have my doubts about whether that will happen.

1 Improvement in global cognitive function, which ought to be
2 fairly easy to do with the neuropsych evaluations that we
3 would do anyway; delay into diagnosis -- actually a delay to
4 the movement into a second impaired domain; and, finally, a
5 differential loss of instrumental activities of daily
6 living. Most of these patients have, as Dr. Petersen said,
7 virtually no functional impairment. The issue about what
8 else is important beside a second domain would clearly be a
9 loss of instrumental activities of daily living, checkbook
10 activities, pill counting abilities and so forth. Thank you
11 very much.

12 DR. KAWAS: Thank you, Dr. DeKosky. The floor is
13 now open for questions. Dr. Katz?

14 DR. KATZ: Just a quick question, you had a slide
15 up that said that the diagnostic criteria for amnesic MCI
16 have predictive validity. Do you mean predictive of
17 Alzheimer's disease?

18 DR. DEKOSKY: Sorry, yes, I should have said for
19 AD.

20 DR. KAWAS: Dr. Wolinsky and then Dr. Ferris.

21 DR. WOLINSKY: Perhaps I missed this, Steve, when
22 you presented those Kaplan-Meier plots. Could you give us
23 some idea of what size populations you were looking at and
24 whether the apparent differences on the right-hand of the
25 curve were real statistically, or are we really looking at

1 the same patient populations moving the same way towards the
2 same end?

3 DR. DEKOSKY: Actually, I believe the latter is
4 true. I am a little surprised -- I am more than a little
5 surprised by that. I think one of the reasons that it looks
6 so homogeneous, and if we control for APO E4 my colleagues
7 tell me that we lose the statistical difference completely
8 between them. Most of the action obviously is in the first
9 five years where they are coming down remarkably together.
10 I couldn't say that that isn't a function of the nature of
11 what comes into specialty clinics. I know when I see
12 patients for Dr. Ganguli out in the Manonga Hill Valley or
13 when we look at patients who come in from the real world, as
14 she puts it, we get much more confusing sorts of cognitive
15 pictures of people and much less reliable kinds of
16 alterations over time. It is one of the reasons why I am
17 really cautious about these data.

18 But within the context of the specialty clinic to
19 which people come, it looks as if these do go down together.
20 I didn't have the N and I winced when I saw that come over
21 on e-mail, that there wasn't an N on there, but this is
22 probably in the range of 60 or 100 patients per group.

23 DR. FERRIS: Steve, in the light of that really
24 nice slide you showed early on that you just got last night
25 which shows, except towards the tail end of time, fairly

1 good similarity between the amnestic versus the broader
2 cognitive decline MCI group, what really would be the
3 utility of making that distinction of the pure memory versus
4 the broader, particularly if in the context of allowing a
5 broader spectrum of very mild cognitive impairment you at
6 least required that one of the domains mildly affected is
7 memory, which is kind of what you do in diagnosing
8 Alzheimer's disease but where the psychometric and ADL
9 impairments certainly are greater in the AD situation?

10 DR. DEKOSKY: What was the question part?

11 DR. FERRIS: The question is what is the utility
12 then of focusing on the pure amnestic group?

13 DR. DEKOSKY: Well, I think the whole concept of
14 this is an emerging one, and I think we have focused on MCI
15 because we can define it fairly easily. It was unique.
16 And, it was actually almost remarkable. We spent 15 years
17 trying to make sure that we could accurately diagnose AD
18 full blown, and when we got up to levels, which I believe
19 all the centers have now, of 90 percent accuracy as
20 confirmed by pathology, we then had all this experience that
21 said, you know, we are seeing a lot of people who come in
22 and they don't quite meet criteria, and one of our criteria
23 for diagnosis is insidious onset and slow progression. Then
24 this light lit up all over the place, perhaps earlier in
25 Rochester, Minnesota when, no doubt, during the winter they

1 are desperate to have more light --

2 [Laughter]

3 -- that, wait a minute -- and in St. Louis as
4 well, there are these cases which, if it is an insidious
5 onset, we ought to be able to find them a bit earlier. I
6 think the easiest definition and, as Ron said, from the
7 pathological driver we know the disease is starting in the
8 medial temporal lobe specifically in structures that lead to
9 hippocampal input, especially entorhinal cortex laminar-2,
10 that was easy to define. It is also one of the structures,
11 hippocampus, that you can do volumetric assessments of, one
12 of the first ones to come to volumetric assessment as
13 opposed to global cortex or specific regions of cortex and,
14 to the extent that you had someone who met their second
15 domain in language versus in visual-spatial, how are you
16 going to decide about doing volumetrics of parietal lobe and
17 so forth?

18 In a variety of ways it made a great deal of sense
19 to me to focus on the amnesic disorder. They also appear
20 to be the most striking separate, different clinical entity.
21 When someone comes in who has very little memory left, and
22 for most of them relatively little insight into the fact
23 that they have a problem with their memory, that is much
24 different than someone who comes in who, if we do testing
25 and then apply age and education norms, turns out to be down

1 in two different areas. Even though the family or the
2 patient may be complaining, they don't quite meet criteria.
3 That is a much more difficult area I think to studies in, as
4 marked by the fact that we pulled those cases out and just
5 watched them over time. We did not have a good protocol on
6 how to do it and we now need to go back and look at the
7 various subtypes of cognitive impairment that we saw.

8 In comment to Jerry's question, I suspect if we
9 move the cut-off for the two domains to one standard
10 deviation below the mean, as opposed to 1.5, I bet we would
11 splay out that MCI other Kaplan-Meier. I bet it would
12 separate a bit more. You could make the argument that 1.5
13 down, you know, they are dangerously close to falling over
14 the edge over the same amount of time but we were struck by
15 how similar they were and that is why I decided to show the
16 slide.

17 DR. KAWAS: I would like to ask a couple of
18 questions. In the individuals who were down in two areas in
19 your MCI other, in what percentage of cases was one of those
20 areas memory?

21 DR. DEKOSKY: That is the other piece I didn't get
22 for the majority of cases, that memory was down as well. I
23 mean, I still think memory is the sine qua non. As you
24 pointed out, we are locked into that as our diagnostic
25 definition. We are trying to find out how many of those

1 cases showed up with, for example, an executive deficit and
2 a language deficit, and it gets into the GINKO trial as we
3 have tried to categorize MCI for the prevention trials but
4 we are accepting MCI cases we have actually split out more
5 kinds of mild cognitive impairments. The singular cognitive
6 impairment that Ron mentioned we have also done, except we
7 have included stroke in that because we think we will find
8 that in a population study. When we would see someone who
9 had a language problem and a frontal dysexecutive problem
10 the question would be did they have Alzheimer's or did they
11 have something else. It is reassuring when they have the
12 memory loss that is the major other domain that we would
13 see, but they just got to us sooner and they are usually
14 highly educated people.

15 DR. KAWAS: My second question is if 60 percent of
16 the patients MCI in your study had Alzheimer's pathology,
17 the other 40 percent had nothing or pathology that looked
18 like AD but wasn't quantitatively adequate, or what?

19 DR. DEKOSKY: We are actually in the process of
20 putting those data together to see how close they got. They
21 had to meet the absolute CERADs to get to a possible AD
22 diagnosis. Of those cases, there were a couple that were
23 clearly said to be not AD, which meant that they had no
24 pathology, but the others under CERAD criteria would be low
25 probability and we are still looking at those.

1 DR. KAWAS: Okay. Dr. Grundman and then Dr.
2 Petersen.

3 DR. GRUNDMAN: I was just going to ask a very
4 similar question to what Claudia had to say about the MCI
5 other. I am not sure that is a great term either because it
6 sounds like that is really more MCI-plus. I mean, you don't
7 know the answer but it sounds like a lot of those cases may
8 have been amnestic plus have some other sort of executive
9 dysfunction, or whatever. In that case, it wouldn't be all
10 that surprising that the two curves are overlapping.

11 DR. DEKOSKY: But to make MCI you had to be two
12 standard deviations down. So, nobody from that group whom
13 we would have called MCI amnestic would be in that group.
14 The other domain had to be above 2.0.

15 But, look, it is a clear sense, looking both at
16 the percentages of conversions of cases we have identified
17 the group of people relatively earlier who appeared to be on
18 their way to Alzheimer's disease that one of the major
19 questions is going to be what are the cases who do not have
20 Alzheimer's disease on their way down?

21 DR. PETERSEN: One issue that comes up that
22 Steve's presentation raised is if you retrospectively go
23 back or if you use more of a neuropsychologically-driven
24 criteria base, you may get a little different answer and you
25 may cut the pie a little differently.

1 DR. DEKOSKY: Right.

2 DR. PETERSEN: For example, in the Karen Richie
3 paper, she did a retrospective analysis trying to retrofit
4 some neuropsychological criteria of cut-off points, standard
5 deviations and the like. While that is helpful, that is not
6 quite the same concept of at least the way MCI was defined
7 in the clinical trials and in some of the prospective
8 studies. There are these clinical criteria, and
9 neuropsychological data are supportive but they do not make
10 the diagnosis in and of themselves. So, you have to be a
11 little careful when you see a study that is just
12 neuropsychologically driven.

13 So, my question for Steve is in the MCI others,
14 what do they complain of or how did they get to you? Is
15 there a subjective appearance different than the MCI
16 amnestic people?

17 DR. DEKOSKY: Frequently, but usually memory or
18 thinking problems is the most -- we haven't done a breakout
19 of what their specific complaints were. We will now. But,
20 remember, at least in our experience a lot of the cases who
21 come in with MCI amnestic are not coming in because the
22 patient is concerned; it is the family who is concerned.
23 The patient usually is not.

24 So, we haven't broken that out but I would like to
25 make a comment about the issue of neuropsych testing. In

1 establishing the criteria for how we would decide when
2 someone had entered MCI or had entered Alzheimer's disease
3 for the GINKO trial, the prevention trial, we made a
4 decision that we would not use the CDR as an endpoint. We
5 will do it in all cases to follow it along and use it as a
6 covariable but in looking at the difficulties that it takes
7 to get accurate and continuous proxy information, we decided
8 that it was going to be way too variable, having looked at
9 some of the proxies and some of the quality of data. So,
10 what we have done is a two-step process. Number one,
11 absolute cut-offs that a neuropsych related, for which we
12 have age and education associated norms to be able to say
13 this person is down to a certain level, followed then by an
14 evaluation by a neurologist and a broader neuropsychological
15 battery. But the biggest problem we had in using the CDR,
16 which we all know can be variable, was that the quality of
17 the information from the proxy becomes another added source
18 of variability and reliability. In our clinic I think we
19 are fortunate because we usually have articulate people
20 coming in and describing what happens, but we all know what
21 happens if, in fact, there isn't anyone reliable to tell us
22 what the story has been with the patient over the past few
23 years. For large-scale trials I think that is an issue.

24 DR. KAWAS: Thank you, Dr. DeKosky. Our next
25 speaker is going to be Dr. Ranjan Duara, who is from the

1 Mount Sinai Medical Center at Miami Beach, Florida, and he
2 will be talking to us about factors that modify conversion
3 rates of MCI to dementia in a clinic-based and community-
4 based study.

5 Factors that Modify Conversion Rates to MCI in a
6 Clinic-Based and a Community-Based Study

7 DR. DUARA: Good morning, everyone.

8 [Slide]

9 I would like to thank Dr. Mani and Dr. Katz for
10 inviting me to this meeting. I think the topic is a very
11 interesting one.

12 [Slide]

13 These are my collaborators. They include, besides
14 those at Mount Sinai, Miami Beach, the Roskamp Institute and
15 Dr. Michael Mullan and Fiona Crawford who did a lot of the
16 APO-E analyses, and also Dr. Peter St. George-Hyslop at
17 Toronto.

18 [Slide]

19 I am going to describe to you the data that we
20 have obtained from two sets of two populations, so to speak.
21 One is basically a clinic-based study. These are patients
22 that have all been examined by me personally over the last
23 ten years or so and in whom I have made a diagnosis. I will
24 describe to you how we make a diagnosis of mild cognitive
25 impairment and subdivide them based on criteria. We had 210

1 patients who met criteria for mild cognitive impairment.
2 You see the age of onset and their mean Mini-Mental score at
3 the time that they were first seen.

4 Based on criteria which I am going to show you,
5 almost 60 percent of them were diagnosed as having early
6 Alzheimer's disease. That was the clinical impression. The
7 mean follow-up interval was 1.9 years, and only about 25
8 percent were actually followed for us to be able to get this
9 data. This is from the overall sample, the 25 percent
10 follow-up.

11 [Slide]

12 The diagnosis of Alzheimer's disease in this mild
13 cognitive impairment study was based on, first of all,
14 excluding all other cognitive factors and other factors that
15 contribute towards a diagnosis of Alzheimer's disease. So,
16 these patients met NINCDS criteria for Alzheimer's disease
17 except that they did not meet criteria for dementia using
18 either DSM-III criteria or the NINCDS/ADRDA dementia
19 syndrome criteria. So, that is the Alzheimer group I wanted
20 to show you.

21 The ones that did not meet the Alzheimer criteria
22 are this group of patients, and in this group we had about
23 37 percent out of the 41 percent of the total that didn't
24 meet Alzheimer criteria and 37 percent had vascular
25 cognitive impairment, 13 percent had psychiatric disorders

1 primarily, and 9 percent had other degenerative disorders
2 such as frontotemporal dementia and Parkinson's disease,
3 then there was another 41 percent that had a variety of
4 other neurological conditions that we thought were actually
5 contributing to the cognitive impairment. That included
6 partial complex seizures and hydrocephalus and a variety of
7 other conditions.

8 [Slide]

9 To diagnose mild cognitive impairment the patients
10 had to have a history of cognitive impairment which was
11 either a subjective history from the patient, from a
12 collateral source or from both. There had to be objective
13 deficits in memory with or without other cognitive domains
14 affected. They lacked DSM-III criteria for dementia and
15 they had preserved functional capacity.

16 [Slide]

17 This is the slide I wanted to show you first,
18 which is that if they met criteria for MCI and they also met
19 all the other criteria for Alzheimer's disease but lacked
20 criteria for dementia, they were diagnosed to have MCI AD.

21 [Slide]

22 To determine whether they had converted from MCI
23 to dementia, basically we needed to have a history of
24 worsening of cognitive function by collateral report. There
25 was worsening objectively in cognitive function measured by

1 psychometrics, and they met DSM-III criteria for dementia.

2 [Slide]

3 This is just to show you what the APE E4 allele
4 frequencies are in this group of subjects that we have
5 diagnosed as MCI AD or MCI other based on the criteria that
6 I just described. For patients who were diagnosed to have
7 probable Alzheimer's disease that are not in the study at
8 all, of which there are 678, the APOE allele frequency is 29
9 percent. For those who we thought had Alzheimer's disease
10 but MCI AD, the frequency was 26 percent. For the other
11 group that we thought did not have Alzheimer's disease the
12 allele frequency was 14 percent. That is pretty close to
13 what we find in our controls population which is 12 percent,
14 the APOE allele frequency.

15 [Slide]

16 Here are the data for conversion to dementia. It
17 is subdivided into two curves according to whether they had
18 a diagnosis of MCI AD or MCI other. As you can see, there
19 is a significant difference in the rate of conversion, with
20 the AD group obviously deteriorating much faster.

21 [Slide]

22 For the entire group of 210, at three years the
23 conversion rate was 47 percent for all MCI. For those who
24 had MCI AD it was 58 percent and for those who had MCI non-
25 AD or other it was 34 percent. That, as I said, was a

1 significant difference.

2 [Slide]

3 Here is the data to show you for all the MCI
4 patients, the effect of APOE on the conversion rate. Here,
5 there is a nearly significant, or a trend to a difference
6 between those who had APOE-4, which is in the red. They
7 have a trend to a more rapid conversion rate to dementia
8 than those who do not have APOE-4.

9 [Slide]

10 Here is the effect of age at which they were first
11 seen, and you see that there is actually no effect at all.
12 You probably can't read what is on the slide at the bottom,
13 but these are three different age groups, in the 60s, 70s
14 and 80s, and there is really no difference.

15 [Slide]

16 This is just a slide to describe what are the
17 biases to our follow-up rate, if any. The only bias was a
18 diagnosis of Alzheimer's disease. If they had been
19 diagnosed to have Alzheimer's disease there was a much more
20 significant chance that they would be followed up but there
21 was no bias in terms of gender, age of onset and so forth.

22 [Slide]

23 To summarize what we found in this group of
24 individuals where we have looked at conversion of MCI to
25 dementia, we found no association -- and I haven't shown you

1 all the data here but these are the conclusions. The age of
2 onset did not have an effect. The use of Aricept was also
3 looked at in a subsample of the patients who were seen after
4 the Aricept was introduced and there was no effect seen.
5 Educational level seemed to have no impact and gender had no
6 impact. The things that did seem to have an impact were
7 diagnosis of Alzheimer's disease clinically in this MCI
8 sample and the APOE-4, whether there was a trend.

9 [Slide]

10 These are the results from a separate group of
11 individuals who were screened from the community. They
12 basically responded to an advertisement put out in
13 newspapers and over the radio and public service
14 announcements. So, it is a completely different sample. It
15 is more or a community-based sample but obviously selected
16 from that as well.

17 These patients were not seen by a physician. They
18 basically had a one-hour screening battery which included a
19 variety of tests, which included the Mini-Mental State and
20 then multiple delayed recalls of the three words in the
21 Mini-Mental after various distracting tasks. We used that
22 as a total score of 12 for their recall on these multiple
23 recalls. We used a combination of the Mini-Mental and their
24 performance on this 4-trial recall to classify patients
25 arbitrarily into those whom we considered normal, those whom

1 we considered to have mild cognitive impairment and those
2 who met criteria for dementia.

3 We have done another study that looked at these
4 criteria objectively and we actually have a paper in press,
5 but I am not going to elaborate on that. I am just going to
6 show you the APOE-4 allele frequencies in this group to show
7 you that there probably is some validity to the way we
8 defined the different groups. The normal group had a Mini-
9 Mental equal to or above 24, plus on the 4-trial recall they
10 got 10 out of 12 correct answers. They had an APOE-4 allele
11 frequency of 12 percent. Those who had mild cognitive
12 impairment had a Mini-Mental equal to or above 24 but a
13 recall score of between 5-9 out of 12, or if their Mini-
14 Mental was below 24 their recall score was greater than 4.
15 They had an APOE-4 allele frequency of 18 percent. Those
16 who were considered demented had a Mini-Mental score below
17 24 and a recall trial score equal to or less than 4, and
18 they had an allele frequency of 26 percent.

19 [Slide]

20 The conversion is shown here. This is really the
21 only data I have in this screening sample in terms of
22 conversion. The MCI to dementia conversion rate, as you can
23 see, is much less than what we get from the clinic sample.
24 At three years 20 percent had converted to dementia using
25 the criteria that I outlined previously. So, this is

1 approximately a half to a third the conversion rate that you
2 see in the clinic sample.

3 In conclusion, what I wanted to say was that I
4 think that one can define MCI using arbitrary criteria. I
5 think that this is an entity that can be diagnosed by a
6 general practitioner or somebody with some expertise in
7 evaluating people using cognitive tests but not necessarily
8 a neuropsychologist. So, there is a portable way of
9 diagnosing MCI, I think, that can be valid and one could set
10 up criteria.

11 The second point I wanted to make was that I think
12 MCI is heterogenous and it really depends on how you define
13 MCI. If you use criteria that are basically used to focus
14 on all features of Alzheimer's disease, then you are going
15 to get mainly patients with Alzheimer's disease at the end
16 who convert to probable Alzheimer's disease. But if you use
17 broader criteria where there are various cognitive
18 impairments allowed, you will find that there is a mixture
19 and that this is not necessarily just a prodrome of
20 Alzheimer's disease. Thank you.

21 DR. KAWAS: Thank you, Dr. Duara. The floor is
22 now open for questions. Will you use the microphone?

23 DR. SHAH: Hi. I am Dr. Shah. Dr. Duara, on your
24 last sample questions you had a Mini-Mental State Exam of
25 less than 24 and they were still considered MCI patients.

1 So, why would that not be considered dementia or early
2 Alzheimer's but MCI?

3 DR. DUARA: Are you talking about the last group?
4 They were demented.

5 DR. SHAH: But before that you showed MCI and
6 there were two divisions. One was Mini-Mental --

7 DR. DUARA: Yes, right. Well, you know, we are
8 looking at a community which is quite diverse in terms of
9 their education and cultural background. Many patients are
10 not necessarily born in the United States. So, we felt that
11 the Mini-Mental cut-off of 24 was not necessarily valid as a
12 criterion for dementia. So, we included those patients with
13 a Mini-Mental of less than 24, however, they had to have a
14 recall score that was above what would be considered the
15 dementia level.

16 DR. PENIX: Your criteria for MCI include
17 objective cognitive deficits on memory and, just as a point
18 of clarification, that objective measure that you used was
19 the MMSE?

20 DR. DUARA: It was a combination of MMSE and their
21 recall scores on the multiple delayed recalls.

22 DR. PENIX: I am beginning to hear a theme from
23 what the past three speakers have presented, that there
24 clearly is an entity of MCI and that it can be identified.
25 The problem I am having is can it be identified by a busy

1 private practitioner or general practitioner in a very busy
2 clinic? The screening tools that you used, do you think
3 that that would be easily used by a practitioner in a
4 general practice?

5 DR. DUARA: No, I don't think it could be easily
6 used by a practitioner. I don't think most practitioners
7 have the time to do this kind of testing. I think it could
8 be done in centers in a metropolitan area, or anywhere, by
9 people who have some training. It certainly can be done in
10 the dementia clinic without the kind of investment that one
11 would put into doing formal psychological testing and
12 evaluation by a physician, and so forth. I think that one
13 could train people to do these kinds of tests and it doesn't
14 require people who have that much education. Somebody with
15 a high school education can be trained to do this kind of
16 testing.

17 DR. VAN BELLE: In your sample of 210, three-
18 quarters of them you only saw at entry and then you did not
19 follow them up at all. You showed at the end that with the
20 Mini-Mental, and so forth, there were no significant
21 differences. But with a three-quarter dropout rate right at
22 the start, I would still be worried about selection bias.
23 Do you have any information at all as to what characterized
24 the dropouts?

25 DR. DUARA: Well, this is basically a dementia

1 clinic and it takes all-comers. The patients aren't asked
2 to commit to a long-time involvement with the center. The
3 people come for a diagnosis; some of them come for repeated
4 -- you know, some patients come from outside the country or
5 outside the state. So, it all depends on the geographic
6 location and their interest in continuing with the center.

7 What I was trying to point out is that I didn't
8 think there was any particular bias other than the fact that
9 if we actually diagnosed them to have a disease that we
10 wanted to treat, we impressed them with that diagnosis; we
11 thought they probably had the beginnings of, say,
12 Alzheimer's disease and then they were more likely to come
13 for follow-up.

14 DR. KAWAS: Any other questions? Dr. Petersen?

15 DR. PETERSEN: Ranjan, given the practice setting
16 of cultural diversity, do you think that adds a whole other
17 level of complexity into this? In what seems might be a
18 subtle clinical diagnosis in the best of situations, is the
19 cultural diversity an additional problem?

20 DR. DUARA: I think it is more representative, by
21 the way, than what is done in a typical university-based
22 research center. I think it is more geared to what a
23 general practitioner or a neurologist or a psychiatrist
24 would see in the community, particularly in this day and
25 age, particularly in a large metropolitan area. This is

1 what you would be exposed to. Does it add challenges? Of
2 course, yes. You are looking at people with completely
3 different backgrounds. That is why we decided, as I said,
4 to change the criteria for the Mini-Mental because we really
5 found from our own studies that the Mini-Mental had a very
6 poor prediction rate for dementia if you used it alone in
7 this community;.

8 DR. KAWAS: Dr. Katz?

9 DR. KATZ: About your criteria for diagnosing MCI,
10 next to the last slide, the MMSE and the recall scores, how
11 do you think that identified patients with MCI compared to
12 other diagnostic criteria that people have used to diagnose
13 MCI? Do you think you identified pretty much the same
14 people?

15 DR. DUARA: These patients who had memory
16 impairment but they could have had a variety of other
17 cognitive impairments as well. So, I think the criteria
18 here are closer to age-associated cognitive decline than
19 they are to MCI as Ron Petersen has described.

20 DR. KAWAS: Thank you, Dr. Duara. Everything is
21 running behind but we can't let that happen to the coffee
22 break so we will reconvene promptly at 10:30.

23 [Brief recess]

24 DR. KAWAS: This is a continuation of the Food and
25 Drug Peripheral and Central Nervous System Drug committee

1 meeting for MCI. Our next speaker is Dr. Steven Ferris,
2 from NYU, and he will be talking to us on mild cognitive
3 impairment as a target for drug development.

4 Mild Cognitive Impairment as a Target for Drug Development

5 DR. FERRIS: It is indeed a pleasure to be here
6 this morning, and I too would like to thank the FDA for
7 inviting me to participate.

8 [Slide]

9 I am going to touch on a lot of the same issues
10 that you have been hearing from the previous speakers, and I
11 am going to try and hone in on a few specific points with
12 respect to syndrome versus a specific disease with respect
13 to some of the specific clinical criteria for MCI and the
14 distinction between MCI as defined in the current array of
15 clinical trials versus a broader conceptualization of what
16 MCI is.

17 This is an old conceptualization that we came up
18 with, and I would have to say that the notion of MCI really
19 began with the first global staging scales for Alzheimer's
20 disease. So, both at NYU in the early 80s and at Washington
21 University in the early 80s with the global instruments, the
22 GDS and the CDR which gradually over time became widely
23 used, there was a classification that kind of fit sort of
24 the grey zone between -- in this case the blue zone --
25 between the normal aging shift in cognition, which is

1 represented here by the shift in the overall spectrum of
2 performance in an elderly group versus a young group, and
3 the emerging criteria at that time for dementia and in
4 particular dementia of the Alzheimer type.

5 So, in both of these global rating scales there
6 was kind of an in between group, GDS 3 and CDR 0.5 back in
7 the early 80s, that really began the thinking about this
8 sort of grey zone, the transition between the normal aging
9 brain impact on cognitive function and the emergence of a
10 dementing disorder such as Alzheimer's disease.

11 In terms of terminology, we have AAMI and ARCD to
12 refer to the effect of brain aging and, as Ron stressed
13 quite correctly, the key in defining these brain aging
14 syndromes is the reference group of performance by young
15 normals, not the reference group of age peers. MCI, on the
16 other hand and, as I understand, AACD which references to
17 standard deviation below age norms, really are overlapping
18 terminologies for this grey zone of MCI.

19 [Slide]

20 This is another way of looking at it. Ron showed
21 a variation on this as well. The key point here is that
22 there seems to be a continuum cross-sectionally between the
23 aging process, MCI and then dementia but, obviously, in
24 terms of what happens long-term longitudinally there is a
25 very important difference between aging brain and a dementia

1 track, here illustrating the fact that MCI is this
2 transition zone between the course of brain aging and the
3 course of a dementing disorder, in this case Alzheimer's
4 disease.

5 [Slide]

6 I would like to start by talking about what I
7 think people have already been referring to as a relatively
8 broad heterogeneous syndrome and some of the more specific
9 underlying etiologies. So, in terms of a broad syndrome,
10 what we are basically talking about -- and I am going to go
11 through this very quickly because I am really repeating what
12 previous speakers have already said -- is a mild degree of
13 cognitive decline that is worse than typical for age but
14 clearly less severe than you see in dementia.

15 This is a point I kind of alluded to in some of my
16 questions earlier of the previous speakers. It involves
17 memory impairment, mild degree of impairment, but in terms
18 of this broad syndrome it also generally includes other
19 cognitive domains, and they tend to be to varying degrees
20 the kind of domains that are also impaired more dramatically
21 in dementia. I think this is quite reasonable since, if
22 this is a prodrome of dementia and if you are talking about
23 really hippocampal changes as being the most obvious
24 structural correlate, there is no reason to expect that it
25 would be selectively isolated, in many cases limited to

1 memory.

2 Another issue is activities of daily living and,
3 clearly, in this general syndrome of mild cognitive
4 impairment the typical everyday activities of daily living
5 are, indeed, intact and if they weren't you would question,
6 well, why aren't you calling them demented. But, on the
7 other hand, there is often subtle impairment in very complex
8 activities of daily living, things like doing your tax
9 returns and so forth. This is really why family members
10 notice that people just aren't performing in cognitive-
11 related complex activities quite as well as they used to do.
12 They are still doing those activities. They are getting
13 them done but there is more difficulty than there was
14 earlier on.

15 As you have heard, it is often a very early stage
16 of dementia, and there are growing number of studies and you
17 have seen some of the data, 10-15 percent per year convert
18 to dementia. It approaches 80 percent over 10 years or
19 longer. And, this is a key point that has been alluded to
20 but I am really going to emphasize it, when, in addition to
21 these general criteria, you use specific inclusion/exclusion
22 criteria that we would use in making a research diagnosis of
23 Alzheimer's disease, except for the severity of the
24 impairments, you generally end up with cases who, in fact,
25 have prodromal AD, and 80 percent of these cases, as you

1 have heard, have hippocampal shrinkage, and that shrinkage
2 is predictive of conversion to AD, and there are a growing
3 number of autopsy series, some published, some not yet
4 published that I have come across, and there is generally a
5 70-80 percent range of individuals who are in this group,
6 the AD type, and I will say more about that in a moment. If
7 they come to autopsy while in this stage, they met CERAD
8 criteria for Alzheimer's disease.

9 [Slide]

10 I won't dwell on this. It is just data from our
11 longitudinal cohort showing the dramatic difference between
12 the normal aging group and the MCI group as defined
13 primarily clinically based on the GDS, and there is almost a
14 six-fold increase in proportion of conversion over about a
15 four-year period.

16 [Slide]

17 Getting back to the point of a broad syndrome
18 versus a specific disease, I think this has been implicit in
19 some of the discussion. It is certainly clear from the
20 interesting data we just saw from Dr. Duara that one could
21 make a distinction between a general heterogeneous syndrome
22 of MCI which progresses often to dementia of one kind or
23 another and a specific disease-based MCI such as MCI of the
24 Alzheimer type, and I would like to strongly suggest that
25 that is, in fact, the most prominent subgroup of the broader

1 syndrome which is, in fact, this transition phase leading to
2 Alzheimer's disease.

3 [Slide]

4 More broadly, this is the way I have modeled it
5 without the advantage of having much data for the broader
6 syndrome and, of course, Dr. Duara just nicely showed us
7 some of the data that I believe fits this model. Embedded
8 in the broad process of brain aging is a subgroup that
9 declines cognitively so that, in broad syndromic terms, they
10 have mild cognitive impairment. They really are comprised
11 of an array of underlying etiologies, Alzheimer's disease
12 being the most common by far; vascular dementia by far the
13 second most common. One could talk about MCI of the
14 vascular type. If you go to vascular dementia meetings,
15 they may not call it MCI but they talk about it. Then, all
16 of the other dementias, including the ones that Dr. Duara
17 listed in his data, are the various other types of
18 progressive dementias, but not necessarily all of them have
19 to be progressive if they are going to lead to an MCI state,
20 and they would be lumped together here. Of course, you have
21 overlaps. You have kind of mixed -- an overlap group, and
22 you may have overlap groups here maybe with the mild
23 cognitive impairment of the AD type with Lewy bodies for
24 example, and so on.

25 An important point, particularly when you go out

1 into the community settings, is that there can be a host of
2 reasons for being in an MCI level of impairment and many of
3 them are stable, and some of these may be reversible. I
4 don't think there is a lot of good data on the size of the
5 stable group, and it probably varies with whether it is a
6 clinic population or community population, and there is
7 back-crossing. We have all seen cases that back-cross.
8 Nevertheless, this is, I believe, a relatively small
9 proportion of cases, perhaps 10 percent or less, in research
10 clinic carefully defined groups where you would be excluding
11 people, for example, with substantial systemic disease that
12 could compromise brain function.

13 [Slide]

14 So, this leads me to suggest that we could define
15 criteria not for MCI broadly, the syndrome, but for MCI of
16 the Alzheimer type. More or less these, in fact, tend to be
17 the kind of criteria that have been implemented in the
18 growing number of MCI clinical trials that are ongoing or
19 about to begin or are planned. This is really fairly
20 compatible with Ron Petersen's criteria, except for allowing
21 more than just isolated memory impairment. I think you
22 should require mild memory impairment but I don't see any
23 reason not to include those who may have very mild
24 impairments in other cognitive areas. Broadly speaking, ADL
25 should be intact but I think you have to allow for subtle

1 impairments in very complex activities of daily living.

2 Of course, if you use global clinical criteria, I
3 think the clinical presentation as the starting point of
4 selecting cases under this rubric should not be just going
5 out and screening with a memory test. It should be based on
6 clinical criteria for MCI as defined reasonably well in
7 either the GDS or the CDR. If you apply inclusion and
8 exclusion criteria for AD, with the exception of the degree
9 of impairment which is obviously much milder, you end up I
10 think with a cohort of MCI of the Alzheimer type.

11 [Slide]

12 I am going to have to speed up. This is our data
13 from our longitudinal work. The data out at 15 and 20 years
14 is really not very reliable but here you see the very
15 dramatic survival curves distinguishing the MCI of the AD
16 type from the normal aging group.

17 [Slide]

18 Another issue is whether you can find markers or
19 predictors, and there is a growing literature -- this is
20 actually an old slide -- relating to relatively large sample
21 studies, longitudinal studies of diverse groups of elderly,
22 sometimes clinic-based sometimes community-based, and the
23 bottom line here is that certain cognitive domains seem to
24 have predictive value for identifying people at high risk
25 for converting to dementia. Memory is obvious. Delayed

1 recall is the most prominent but other domains, such as
2 attention and language function also seem to emerge.

3 [Slide]

4 Just quickly, this is data from our cohort
5 suggesting that a relatively small number of cognitive
6 measures, the most prominent being paragraph delayed recall,
7 shows very good overall accuracy of predicting conversion
8 over about a four-year interval to AD.

9 [Slide]

10 If you look specifically at the most powerful of
11 these tests, our delayed paragraph recall test, there is
12 about a 90 percent accuracy, overall accuracy. These are
13 sensitivity and specificity curves for outcome of predicting
14 conversion to AD. The caveat here, of course, is that this
15 is a carefully selected clinic-based sample. Whether this
16 would produce similar accuracy in community settings is
17 probably unlikely.

18 [Slide]

19 This is just to make the point that the delayed
20 recall variable seems to relate fairly well to a structural
21 measure in the brain, the hippocampal volume and, it turns
22 out that individuals with greater hippocampal shrinkage show
23 greater longitudinal decline over a few years in delayed
24 memory. So, there is a tie-in in our predictions between
25 the structural measure and a memory measure such as delayed

1 recall.

2 [Slide]

3 The final point gets to the issue of what do we do
4 about targeting this syndrome in clinical trials. I won't
5 go into much detail here but some of us, going back ten
6 years, realized that the MCI group seemed to provide a nice
7 bridge between the traditional symptomatic trials in people
8 with Alzheimer's disease and what down the road we want to
9 accomplish, primary prevention in large community-based
10 studies. Since conversion rates are so much higher, this is
11 a very at risk group for subsequently obtaining a diagnosis
12 of Alzheimer's disease. It is really an ideal model sample
13 for looking at the potential effect of pharmacologic agents
14 for delaying that endpoint. This, of course, is not a
15 prevention trial. It is really, at best, a disease
16 progression trial, although on the clinical data alone you
17 really are showing an effect on clinical progression rather
18 than disease progression. You can also look at rate of
19 cognitive decline in addition to or instead of time to
20 clinical diagnosis.

21 As has already been mentioned in the questioning,
22 the interpretation of progression certainly can be
23 confounded by direct symptomatic effects. On the other
24 hand, if you saw an effect on conversion without a parallel
25 treatment effect on cognitive symptoms I would consider that

1 very unlikely. Of course, you have heard from Ron about the
2 utility of MRI measures, and in these clinical trials a
3 useful adjunct to the clinical measures and cognitive
4 measures, to a growing extent, is to look at objective
5 measurement of hippocampus or whole brain as a biological
6 marker that could support a potential claim as a result of
7 the clinical effects of progression from MCI to AD.

8 [Slide]

9 It is very important in terms of designing these
10 clinical trials to include objective screening to do three
11 things: to objectively confirm that there is, indeed, mild
12 memory impairment. This is part of most definitions of MCI
13 to start with. It is likely to increase the proportion of
14 cases who, in fact, have prodromal AD as opposed to a
15 different etiology, and it is possible, as you saw from the
16 paragraph recall data, to enrich a study population with
17 respect to overall risk for conversion over the observation
18 interval.

19 [Slide]

20 This is data from the ADCS, which probably Mike
21 Grundman will talk about in greater detail, showing the
22 ability of setting a memory cut-off score in longitudinal
23 data, the ability to artificially increase the rate of
24 conversion by comparing people above or below a particular
25 memory cut-off.

1 [Slide]

2 These are some of the screening tests -- I am not
3 going to talk about them -- that have been actually used in
4 ongoing clinical trials. A common feature is memory and, in
5 particular, delayed memory.

6 [Slide]

7 One of the issues put before us today was whether
8 there are any unique requirements in MCI trials with respect
9 to outcome measures. You have heard about the conversion to
10 AD survival design where AD is the primary outcome. There
11 is no reason not to incorporate into clinical trials the
12 same domains of assessment that have come to be fairly
13 standard in Alzheimer trials. Of course, cognitive function
14 and global status and ADL are the three most important and
15 most directly representative of the emergence of dementia
16 and of the decline you see in MCI. Most people now strongly
17 recommend including objective measurement of brain structure
18 using MRI, and we would love to have a blood test that not
19 only was a reliable marker for disease but that was also
20 changed over time as a correlate of brain decline but, at
21 the moment, hippocampal or whole brain atrophy, for that
22 matter, appear to be the best markers for use in clinical
23 trials.

24 [Slide]

25 I have listed the domains that I think are useful

1 for measuring outcome in MCI trials but there are some
2 special considerations. It is not necessarily the case, and
3 generally not the case, that the best measures are the same
4 measures that have long been used in Alzheimer trials. I
5 think the cognitive battery in particular must be
6 specifically tailored for sensitivity range to normal aging,
7 MCI to early AD.

8 That being said, the tried and true ADAS-COG is
9 simply not a sensitive enough measure, for a variety of
10 reasons, for MCI trials. Most of the MCI trials that have
11 been launched actually have implemented a more sensitive MCI
12 cognitive outcome battery.

13 Similarly, global and ADL instruments need to be
14 modified, as in some cases they have been, particularly by
15 the Alzheimer's Disease Cooperative Study. The typical ADL
16 and global instruments need to be modified to specifically
17 focus more directly on the very early impairments, the more
18 subtle impairments in functioning and in global status that
19 are commonly seen in MCI and as MCI makes the transition to
20 dementia.

21 So, the bottom line is that to some degree a lot
22 of work has already been done and implemented in developing
23 or modifying instruments that are tailored specifically for
24 use in MCI trials. So, we can measure outcome appropriately
25 in these trials.

1 [Slide]

2 Finally, just to conclude, in answer to one of the
3 key questions, MCI broadly speaking is a heterogeneous
4 syndrome. However, homogeneous groups representing
5 prodromal AD or other subtypes can, I think, reliably be
6 identified. MCI trials can examine disease progression or
7 at least clinical progression and provide a bridge in drug
8 development between symptomatic trials and the ultimate goal
9 of disease prevention trials. Suitable outcome measures for
10 MCI trials are available. With respect to what the FDA is
11 going to do with this with respect to labeling, if there are
12 great results from some of these MCI trials I would suggest
13 that labeling for specific prodromal dementias, such as MCI
14 of the AD type, is appropriate.

15 DR. KAWAS: Thank you, Dr. Ferris. The floor is
16 now open for questions. Dr. Katz?

17 DR. KATZ: Yes, I have a question about the
18 heterogeneity, the presumed heterogeneity of MCI. You had a
19 slide up there -- I don't know if it was data-based or
20 theoretical but you talked about how global MCI could
21 progress to dementia, other types of dementia, other than
22 AD. Then you have your MCI of the Alzheimer's type which
23 presumably progresses pretty much uniformly to Alzheimer's
24 disease. We have seen other data that suggest that it
25 doesn't really matter who you include in the MCI category,

1 they pretty much all go to Alzheimer's disease. There was
2 Dr. DeKosky's data where amnestic MCI, I believe, was in the
3 "other" and they all seemed to go to Alzheimer's disease.
4 Then, Dr. Petersen had data which suggested that if you
5 limit the definition to the amnestic MCI, they almost all go
6 to Alzheimer's disease.

7 So, I am just wondering how your theoretical
8 construct about it being heterogeneous and perhaps going to
9 other dementias comports with the other data that we have
10 seen, which suggests that whichever subgroup you look at
11 they go to Alzheimer's disease.

12 DR. FERRIS: Well, I will begin to answer that
13 question by reflecting on a typical question you get from
14 families who have brought a patient in. The question they
15 ask is, "I don't understand. Somebody told me he had
16 dementia; somebody else told me he had Alzheimer's disease.
17 What's the difference between dementia and Alzheimer's
18 disease?" So, I give the same answer to the question of
19 what is the difference between MCI of the Alzheimer type and
20 MCI more generally. One is a general syndrome. I mean, we
21 all know what dementia is, and it is definable, but it is
22 heterogeneous. I would say that MCI generally is
23 essentially the same as dementia generally, and that the
24 task before us is to be more specific about how we define
25 this subtype of this more heterogeneous group.

1 The reason, in a lot of the data that you have
2 seen, that most of the people who convert, convert to AD is
3 by virtue of what happens at the front end of the subject
4 selection process. You are starting generally with people
5 who are carefully worked up and there is a tendency, at
6 least in much of that data -- I am not saying all, to
7 exclude from the group you follow people that have had
8 strokes; people that have serious systemic illnesses or
9 Parkinson's or signs of Parkinson's syndrome. So, those
10 people, when they are in their prodromal state, they are not
11 included in the cohorts that are being followed which show
12 such a high proportion of cases that specifically convert to
13 dementia of the Alzheimer type.

14 You saw Dr. Duara's data which was a broader
15 spectrum and you got a different kind of result. AD was
16 certainly the most predominant outcome diagnosis, but you
17 had all the other stuff in there as well. I think that is
18 what you would find in a true community-based study, and
19 maybe we will see more of that data before the day is
20 through.

21 DR. KAWAS: Actually, I have a question, Steve.
22 You showed paragraph recall, digit spans and things, having
23 to do with memory and attention primarily, as four tests
24 that are useful for predicting these subjects. Are these
25 tests that you would propose be used out in the clinic to

1 identify individuals if we did have a drug with an
2 indication for MCI? If so, you mentioned that this wouldn't
3 work as well out in the clinical environment. So, what do
4 we do about that?

5 DR. FERRIS: What I am saying is I think in the
6 clinical setting these kinds of measures -- I think the
7 domains that jump out at you are, first and foremost, memory
8 but attention concentration measures, the more sensitivity
9 among the language measures and certainly executive function
10 measures tend to be sensitive as well. What I simply meant
11 by that is that you have a healthy, carefully selected
12 cohort in which this prediction data emerges. Out in the
13 community-based setting, if you just went out and screened,
14 not at clinics or doctors offices or whatever, but if you
15 went to apartment houses, or whatever, and screen people
16 what you would find is all sorts of systemic diseases, all
17 kinds of other issues that can compromise brain function
18 and, consequently, in terms of the broad syndrome definition
19 might meet criteria for MCI but they are not necessarily
20 going to progress to Alzheimer's disease. So, the
21 proportion who have Alzheimer's and the proportion that
22 actually progress, I am guessing, is probably going to be
23 lower out in the community setting. But in terms of
24 carefully selecting cases, I think this sort of data is
25 obtainable.

1 DR. WOLINSKY: I guess one of the things that I am
2 struggling with is not the issue as to whether mild clinical
3 impairment is stage I Alzheimer's disease, or whatever you
4 want to call it. That seems to be a case very well made.
5 But if you could actually construct a trial and were lucky
6 enough to have a pharmacologic agent, carried out in careful
7 clinical settings, that actually delayed the progression
8 from phase I to phase II, or whatever we call this, and the
9 person on the street can only diagnose phase II and we don't
10 know whether starting the drug at phase II will prevent
11 progression to phase III, what do we then do when we have a
12 drug for which no one can make a diagnosis except in very
13 rigorous, well-defined confines?

14 DR. FERRIS: Well, you know, five years ago or ten
15 years ago you had the same issue with respect to treating
16 Alzheimer's disease. In the community settings the level of
17 expertise for applying reasonable criteria to make a
18 diagnosis of Alzheimer's disease were not what they are
19 today. There has been an evolution in terms of education
20 and training out in community settings so that just as
21 Alzheimer centers now have 95 percent accuracy, community
22 settings have probably gone up from 60 or 70 percent
23 accuracy up into the 80s perhaps. I think the same
24 situation would pertain to MCI. There will have to be a
25 process of education, just as there was in the case of

1 Alzheimer's disease, that enables Alzheimer type criteria to
2 be applied to the MCI syndrome. Since community settings
3 can now apply Alzheimer criteria to people with more serious
4 impairments, I don't see any reason why the same occurrence
5 wouldn't apply in the case of MCI of the Alzheimer type.

6 DR. WOLINSKY: Forgive me, maybe I am lost in the
7 semantics but I thought we had drugs which symptomatically
8 improved some of the target symptoms of Alzheimer's disease.
9 I didn't know we had any that actually prevented progression
10 of Alzheimer's disease.

11 DR. FERRIS: That is correct.

12 DR. WOLINSKY: So the question I had was a little
13 bit different. Coming from a slightly different therapeutic
14 area where we were lucky enough to develop some drugs in
15 well-defined disease and then have recently moved that to
16 earlier definitions of disease is one way to take therapy
17 development. Moving in the other direction is more
18 difficult because disease may become harder to treat as it
19 progresses.

20 DR. FERRIS: Sorry, I am still not clear on the
21 question then. I am sorry.

22 DR. WOLINSKY: The question is if you have
23 something that works very, very early can you then assume
24 that it will have any benefit late.

25 DR. FERRIS: I think every study has to stand on

1 its own and be interpreted based on the population selected
2 in that study. I don't think you can assume anything. In
3 other words, because we now have drugs that treat
4 Alzheimer's disease, at least symptomatically, we cannot
5 assume that those drugs are also effective in prodromal AD.
6 We have to do the trials, and the trials are being done.
7 But if those trials are done and the data are accepted, then
8 one would be able to conclude that a particular drug has
9 symptomatic benefits in MCI of the Alzheimer type.

10 The issue of whether you are affecting progression
11 is a more difficult question and you have the same
12 difficulties in generating data to support that kind of
13 claim in AD or MCI. You have exactly the same issues,
14 exactly the same possibilities for designing trials
15 differently and the same hope for biological markers to help
16 you support an effect on clinical progression on the basis
17 of a biological marker.

18 DR. KAWAS: Dr. Katz and then Dr. DeKosky.

19 DR. KATZ: Yes, there has been a lot of talk about
20 this time to diagnosis or progression to diagnosis of
21 Alzheimer's disease. I think that trial, and I think we
22 think that that trial, if it were done, would merely
23 document a symptomatic effect on symptoms. It could
24 possibly be documenting an effect on progression of the
25 underlying disease but I don't think you could tell that

1 from that design. You would have to do other maneuvers.
2 So, I think if it is just time to diagnosis of frank
3 Alzheimer's disease we would interpret that as a design that
4 was really only capable of detecting a symptomatic effect.
5 So, I don't want to get confused talking about a treatment
6 that did that as one that had an effect by definition on the
7 underlying pathology. We would not interpret that trial
8 that way.

9 DR. FERRIS: Well, I would agree with you that you
10 could not interpret that as telling you about underlying
11 pathology but I think, depending on the way the study is
12 designed and depending on how the data came out and how you
13 described the results, objectively you could describe an
14 effect on clinical progression in the sense that you started
15 out at one level of impairment and you ended up at another
16 level of impairment. Where you ended up, hopefully, is
17 different between a placebo arm and a treatment arm, and you
18 can describe those results.

19 I would be worried, for example, if you saw an
20 effect on time to conversion but didn't see an effect on
21 actual objective measures of cognitive performance and
22 functioning, for example. But if you showed a treatment
23 effect on both, it would suggest to me that the clinical
24 course of the disease, particularly if you had a slope
25 difference, is affected by the treatment.

1 Now, it would absolutely be a leap to imply from
2 that that you have affected the level of pathology in the
3 brain because you have no data to show that. However, if
4 you added into such a trial and you got the wonderful
5 results I just described, and you had longitudinal objective
6 MRI data showing less hippocampal shrinkage, further
7 hippocampal or whole brain atrophy measurements over the
8 course of the trial that seemed to parallel the clinical
9 progression difference, I think you are beginning to create
10 a circumstantial case or at least a convergence of evidence
11 that it may be more than just symptomatic.

12 DR. KAWAS: Would you still feel that way if the
13 drug was withdrawn and the person went back to placebo
14 levels?

15 DR. FERRIS: Probably not.

16 DR. DEKOSKY: I wanted to make a comment on Dr.
17 Wolinsky's question. We have at least one medication that
18 we think is probably not effective in treatment of AD but
19 still holds hopes for prevention or delay in entry of people
20 into Alzheimer's disease, and that is estrogen. There are
21 two studies that suggested it has not been very helpful, and
22 a wealth of epidemiological data that suggest that there is
23 a difference, although there may be other reasons for it and
24 that is why the subsequent trials. There are also
25 pathological changes that occur during the course that

1 suggest you may be able to fix some things but not others.

2 My reason for bringing up the choline
3 acetyltransferase data was to suggest that in the early
4 course of the disorder if you find something to stop or slow
5 down the progression of disease there is more work than we
6 thought there was when we defined the disease by what we saw
7 at end-stage burnout.

8 But from the standpoint of separating this
9 pathological alteration that Dr. Katz was talking about from
10 what we see when we test people in the clinic, my personal
11 belief is that the cholinergic drugs won't improve memory
12 function. I think that is borne out to some extent by the
13 data from the drug company studies themselves that say that
14 attention-concentration and a variety of other things are
15 the major things that appear to push the improvement that
16 people see, especially the family members. If you look at
17 the pathology of those people, what you see is devastation
18 of their entorhinal cortex with massive tangle formation in
19 the projection neurons to the hippocampus, the way the
20 hippocampus gets its information about what is going on for
21 recent memory, and we see relatively intact levels of
22 choline acetyltransferase. It doesn't mean the system is
23 functional but it means the enzyme is still there. But if
24 the primary inputs are not there any longer, then pushing
25 the cholinergic system for memory probably isn't going to

1 make much of a difference.

2 It is my view that if you get people who are
3 symptomatically severely impaired with memory, the chance
4 that we can make them better or improve them significantly,
5 other than a bit by enhancing attention-concentration and
6 that component of memory -- I don't think we can improve
7 them very much. However, we have the rest of the
8 improvements in some of the new longitudinal studies with
9 some of the other esterase inhibitors in suppression or
10 delay of emergence of some of the other symptoms. Now, they
11 are symptom emergence. No one makes the argument certainly
12 among most of the biologically based people here that this
13 reflects provable changes in the course of the disease. But
14 from the standpoint of what people look like -- whoever
15 devised the term "slows apparent clinical progression"
16 probably gets the prize, probably a marketing person but, in
17 fact, that is the description.

18 Perhaps the model that we are struggling to come
19 to here is more related, Dr. Temple, to Parkinson's disease
20 than it is to cholesterol hypertension risk state.
21 Parkinson's patients are much more strikingly improved by
22 their drugs but the progress of the disease, insofar as we
23 can tell, isn't affected. And, it may well be that the use
24 of these drugs in this condition is a similar sort of
25 symptomatic boosting or a preservation of function and a

1 lack of decline of other pieces that reflects the purely
2 symptomatic approach but which, in a clinical state, has
3 some significant benefits.

4 DR. KATZ: As I said earlier, semantics is
5 everything. One of the reasons we don't like to use the
6 word progression when we are describing what we believe to
7 be a symptomatic effect is because it tends to imply that
8 there is an effect on the underlying progression of the
9 disease. But, you know, that is a discussion we could have
10 but that has sort of been the take that we have had on it.

11 But under the heading of semantics, let me ask
12 you, Steve, the same question I asked Dr. Petersen. I know
13 you won't be around for the discussion period so I would
14 like to get your opinion, and it is an opinion, I recognize
15 that. At least for the patients that have been enrolled in
16 trials of MCI which you are calling of Alzheimer's type, you
17 have referred to those patients as having prodromal AD.
18 That is a slightly different word and implies perhaps
19 different things than a term like early Alzheimer's. We
20 know these patients don't have Alzheimer's disease by
21 definition, but in your opinion, as an expert, would you say
22 that these patients have, let's say, pathologically early
23 Alzheimer's disease?

24 DR. FERRIS: Yes.

25 DR. KAWAS: Dr. Temple?

1 DR. TEMPLE: I suppose one could make the case
2 that these groups, defined the way they are and indicated by
3 the survival curves for dementia, you could perhaps
4 characterize these people as ones who are very likely over a
5 relatively short period of time, like six months to a year,
6 to progress to symptoms that are disturbing and will disturb
7 them and their family, and that sort of prophylaxis against
8 that, even if you are only preventing the symptoms that will
9 emerge, might be considered a benefit perhaps for a very
10 safe kind of drug because you are putting it in there before
11 they have those symptoms. I guess one could make that sort
12 of case. It is a little unusual.

13 DR. FERRIS: But another point, and it gets back
14 to when you raised this question earlier this morning, is
15 that it is not quite the hypertension analogy where, as I
16 understood it, you are starting with people who have
17 perfectly normal blood pressure. In this instance you are
18 not starting with people who have normal cognitive function.
19 They do have mild impairment. So, a symptomatic benefit in
20 this group, even if you ignore the whole business of is it
21 progression or not, is a potential benefit because if they
22 are able to function cognitively a little bit better and,
23 relative to their age peers, they start out when they enter
24 the trial, being worse than normal. So, I don't see any
25 problem with a symptomatic treatment for this group.

1 DR. TEMPLE: No, I don't think we have ever
2 challenged that. I guess the question is where you can't
3 for one reason or another actually detect a symptomatic
4 improvement as you are going along but at some time point,
5 much later, it turns out they have a lower incidence of
6 documented dementia, what exactly is that? But, again, I
7 think we are pretty open on all of these.

8 DR. FERRIS: Yes, and the other thing is, you
9 know, it is all arbitrary where you end your measurements.
10 I mean, if you had a purely symptomatic effect, no question
11 it could affect the endpoint of conversion, but not if you
12 waited 15 years if it were a purely symptomatic effect.

13 DR. PETERSEN: I was just going to underscore
14 that. These people are not asymptomatic like in the
15 hypertension group, and there is a certain amount of
16 inconvenience and problems that are presented by the memory
17 problem itself.

18 DR. TEMPLE: But there was expressed skepticism
19 that many of these drugs would improve that. I mean, if
20 they did improve it you wouldn't hear any debate at all
21 about the question. I mean, suppose they didn't but
22 prevented things that haven't really appeared yet --

23 DR. PETERSEN: I would think that is beneficial in
24 and of itself also. So, if they got symptomatic improvement
25 in their major symptom, that is good. But even if that does

1 not improve but you prevent or slow down the appearance of
2 other symptoms, that too is worthwhile.

3 DR. DEKOSKY: I don't think that is terribly
4 different than the situation in which we find ourselves
5 clinically with these drugs in AD. You know, the early
6 expectations that these medications would produce an L-dopa
7 like effect wasn't realized, and what we have learned after
8 five or so years of using them is that if you keep people on
9 the medications there is, in fact, a benefit to the entire
10 population in that there is a slowed emergence of symptoms
11 or there is maintained higher function.

12 But one of the things we don't usually see, or we
13 see it in my experience less than 15 percent of the time, is
14 this sudden upsurge in cognitive function. But the
15 separation does not occur between placebos, for example, in
16 my experience, and the drug-treated groups in double-blinds
17 by a leap up in function but, rather, by kind of a slowing
18 out and then a decline and then these things are in
19 parallel.

20 So, in fact, I am not sure this wouldn't be a
21 relatively similar sort of thing. You might not see an
22 improvement in memory function. You might see a slight one
23 in the cause of the cortical benefits, other systems that
24 aren't as devastated this early in what you think is the
25 pathological decline to AD. But we are actually used to

1 thinking about that now in terms of the symptomatic
2 protection of the individual manifestations of the disease.

3 I guess I hadn't really thought about it in terms
4 of it being purely semantic. Perhaps we are being very
5 pragmatic about it but there is a biological basis to it as
6 well. We are not sure why people didn't suddenly have a
7 kick up in 90 percent of cognitive functions and have that
8 be the separation between improved cognitive function in
9 patients on drug versus those on placebo, but they do almost
10 all separate out. In many cases it is just maintenance.
11 These are data you have seen a lot of. It is maintenance of
12 where they are as opposed to decline. In the case of
13 holding them at just one cognitive impairment and not
14 leading them especially into instrumental ADL alterations
15 and spatial disorientation pieces, that I think is the
16 perceived benefit of this even though we are on this thin
17 ice of the difference between calling it a purely
18 symptomatic effect and somehow implying that it actually has
19 a biologically interventional effect.

20 DR. KAWAS: Actually, can I ask Dr. Temple a
21 question to educate me and the panel? I think that
22 everybody chooses examples that, if nothing else, do a good
23 job of disclosing where they are coming from. So, I don't
24 think actually the hypertension is a good model. First of
25 all, it is not symptomatic and all the other reasons people

1 said. But I also don't think that L-dopa and Parkinson's
2 disease is a good model because that clearly has a dramatic
3 symptomatic effect.

4 But the model that strikes me as being most
5 relevant to what we are discussing here today might be
6 selegiline or Deprenyl in relationship to PD. There is a
7 drug which was designed to look at least at the possibility
8 that it delayed onset of the disease. In fact, the
9 interpretation was complicated probably by the fact that
10 there is purely or possibly only a symptomatic effect that
11 generates that delay rather than a disease-altering course.
12 And, I don't really know the FDA's position on that
13 particular situation and how that drug fits into this model.

14 DR. TEMPLE: Russ can probably tell you better
15 than I can. I believe we do not believe that selegiline
16 does anything more than treat symptoms of whatever degree of
17 disease you have at the time you have it. That will, of
18 course -- and that is what we have been talking about --
19 always look like it is delaying the onset of any given
20 severity. If you don't like hypertension, give me heart
21 failure. If you put everybody on a diuretic and they have a
22 progression heart failure disease they won't look as bad at
23 any given time but you might treat them for five years
24 before they would have looked bad in the first place. So,
25 the question is, to me, whether you wait to treat a symptom

1 that has been developed and show that you can treat it, or
2 whether you get the drug in there early.

3 Again, I just want to emphasize no one has any
4 doubt at all that if you made some component of cognitive
5 function get better or decline less fast, and that was
6 detectable, that would be of benefit. I don't think that
7 anybody has any doubts about that. Say it was really true
8 that these drugs had no effect on memory components, which
9 are the way you have entered people into the trial, but only
10 prevented other things that accumulated later, as we watched
11 those life table curves, the question then would be when
12 should you start a drug like that? When you have those
13 other things or earlier? You know, I don't think it is out
14 of the question that you would say it is so devastating;
15 these things sneak up on you; it is so bad for your life and
16 for your family's life that knowing these people are likely
17 to get that you might want to get the drug in early. I
18 mean, I certainly wouldn't reject that. Maybe it is very
19 reasonable. Nor would anybody, by the way, doubt that if
20 you actually changed the anatomy and improved MRI that that
21 would be worthwhile. I don't think that would even be
22 controversial at all. But if all you are doing is treating
23 a symptom, should you wait until the symptom emerges before
24 you treat it? That is really the only question I am
25 raising. I think the heart failure is not a bad example.

1 DR. KAWAS: In the case of MCI the symptom, to
2 many people's mind, has emerged -- memory loss.

3 DR. TEMPLE: And if you treated the memory loss no
4 one would argue at all. But we are hearing that maybe you
5 don't expect very much on memory loss. I mean, I don't
6 know; we haven't seen the trials.

7 DR. DEKOSKY: That is my hypothesis. I don't know
8 that but we need to find that out. That is what some of the
9 trials, I believe, are expected to look for.

10 DR. TEMPLE: Okay, but we wouldn't even argue that
11 point. I mean, if you improved the memory loss that is the
12 basis for the diagnosis that would be a benefit. Right?
13 That wouldn't be a debate.

14 DR. FERRIS: I think that if you showed an effect
15 on time to endpoint, such as conversion to AD, and didn't
16 show a treatment effect on cardinal symptoms of AD that
17 would be a problem in interpreting the outcome. But I would
18 be quite surprised if you got that outcome.

19 DR. KAWAS: I am not sure I should go there but
20 why would you be surprised since we have already done that
21 before in previous studies where we improved time to
22 outcomes without improving the cardinal symptoms we thought
23 should get us there?

24 DR. FERRIS: Well, there are measurement issues in
25 severe AD which confound your ability to measure certain

1 outcomes like cognitive function.

2 DR. KAWAS: And, are the measurement issues in
3 early AD which confound our ability?

4 DR. FERRIS: I believe the memory measures, for
5 example, are sensitive enough to pick up movement
6 longitudinally from MCI to AD, and many of us have been
7 looking at data on individual cases from individuals deemed
8 to have converted in MCI trials -- I am speaking very
9 generally, and it is fairly rare not to see other clinical
10 measures get worse relative to baseline when a clinician at
11 a site deems an individual to have converted on the basis of
12 that dichotomous endpoint. I partially base my expectation
13 on observing a lot of this sort of data, of course, in
14 totally blinded ways.

15 DR. KAWAS: Dr. Penix and then Dr. Katz.

16 DR. PENIX: If a drug were found to prolong
17 conversion to AD, are there not objective indicators, such
18 as loss of independence or prolongation of time to nursing
19 home placement, that may show that that single benefit is
20 beneficial overall as opposed to just treatment of the
21 symptoms?

22 DR. FERRIS: Nursing home placement is an
23 interesting outcome. It is just that in an MCI trial, when
24 you are just crossing the threshold to AD you are not likely
25 to have enough occurrence of that outcome to really analyze

1 it. But you do have ADL instruments. You do have cognitive
2 batteries and other outcome measures that ought to parallel
3 the dichotomous outcome of conversion. I would have to
4 agree with Rusty that if you didn't see that in an MCI trial
5 it would give one pause.

6 DR. KAWAS: Dr. Duara, and then we will move on to
7 Dr. Ganguli's talk.

8 DR. DUARA: I just wanted to emphasize that I
9 think that this whole issue about looking at the symptomatic
10 effect of any medication that one uses to treat memory
11 impairment -- if one uses the rate of conversion to
12 dementia, you are automatically handicapping yourself. It
13 is so variable, this whole issue about who diagnoses
14 dementia, at what point, that you are just adding another
15 wild card into the whole game and decreasing your ability to
16 actually measure the effect. I think the only thing that
17 should be done is to look at the symptomatic effect of the
18 drug in terms of cognitive testing.

19 I think the reason why we are looking at
20 progression to dementia from MCI is more a political one
21 than really a biological one because AD has a certain impact
22 -- now you have Alzheimer's disease. But that is really not
23 the scientific question because all the data that has been
24 shown has shown that already the patients with MCI are
25 pathologically, in many cases, indistinguishable from

1 patients with Alzheimer's disease if they have that
2 Alzheimer type of MCI. So, why are we looking at this
3 particular conversion rate as the index? It is actually
4 handicapping us in terms of measurement. It is adding a lot
5 of variability from center to center and in our ability to
6 measure this.

7 DR. KAWAS: Thank you. Dr. Katz?

8 DR. KATZ: I think the value, at least in the
9 cohorts that we have seen so far which have looked at
10 conversion rates to Alzheimer's disease, the value of it is
11 in helping to further understand what MCI is. As an outcome
12 measure in a trial you can argue whether or not it is a good
13 or a bad one for a lot of different reasons. I think that
14 if you use it, it is an outcome that would allow you to
15 document a symptomatic effect at least. The question of
16 whether or not it is a good idea or a bad idea to use it, or
17 a good idea or a bad idea to treat patients before certain
18 symptoms develop is a separate question. But I think here
19 it is critical to look at conversion to Alzheimer's disease
20 because it tells you what the natural history of MCI is and,
21 by inference, what MCI might very well be.

22 DR. KAWAS: Dr. Temple?

23 DR. TEMPLE: But the point being made was that
24 almost all the time when you enter people into a study
25 because of a particular symptom you are most likely, if the

1 drug works, to be able to show an effect on that symptom
2 because all the people in the trial have it and you are
3 focused on it. Whereas, if you look at other things you
4 would have to be either very lucky and you would have to
5 overcome the variability in diagnosis, or if you really
6 expected an effect on memory particularly you would
7 certainly want to go for that because you are most likely to
8 succeed because all the people have it. It is like all
9 these quality of life scales we see all the time where
10 people are entered who don't have impaired quality of life
11 so nobody finds anything and everybody is surprised.

12 DR. KATZ: I agree, but my only point is that if
13 they were to show such an effect on conversion it is a
14 finding that is probably clinically meaningful and at least
15 is real.

16 DR. DEKOSKY: I just have to add that I must
17 disagree with Ranjan, a situation I don't find myself in
18 very often. I think the consistency of the conversion rates
19 when these diagnoses are used is remarkable. I have another
20 slide on the the class I evidence for conversion and just
21 about everyone is ending up with conversion rates between 12
22 and 15 or 16 percent per annum in these groups. I mean,
23 they may be slightly variable in their definitions but they
24 are remarkably consistent in their conversion rates. I
25 think that is telling us something about the fundamental

1 biology that is a good place to begin to look for other
2 kinds of things that affect structure. But if you can push
3 these conversion rates back with these medications, my own
4 belief is that would be a useful thing.

5 DR. GRUNDMAN: The other point is that I think the
6 reason most of the trials are using AD as an endpoint is,
7 number one, because it has face validity; it has clinical
8 relevance. Whereas, a change on a cognitive measure alone
9 might not be clinically relevant in the absence of some
10 other clinical detection. Also, in fact in all these trials
11 we are looking at cognitive measures and ADL measures and
12 they are all being assessed in addition to the primary
13 outcome which is conversion to AD.

14 DR. KAWAS: Thank you. Dr. Mary Ganguli, our next
15 presenter, will be talking to us about mild cognitive
16 impairment: a view from the trenches. She is from the
17 University of Pittsburgh.

18 Mild Cognitive Impairment: A View from the Trenches

19 DR. GANGULI: I owe my presence here to the FDA
20 and to the National Institute on Aging. In interest of full
21 disclosure, also to the manufacturers of Immodium, who may
22 or may not be present --

23 [Laughter]

24 I also thought I was being invited to participate
25 in a Ron Petersen celebrity roast. It hasn't quite turned

1 out that way but I need to start by reassuring Dr. Petersen
2 that I am his number one fan. The only thing we disagree
3 about are some of Mario Lemieux's qualifications for
4 immortality, but he is from Minnesota and you have to
5 understand that.

6 I am a psychiatrist and an epidemiologist, and I
7 think today I am primarily here as a clinician in the
8 trenches. I will try to keep the epidemiology from creeping
9 in but it will from time to time.

10 I personally do not believe it is going to be cost
11 effective for industry to push for this claim for MCI if it
12 is only going to be diagnosed in the kinds of people who
13 show up in Alzheimer's centers. I do believe that those
14 people aren't, I wouldn't say are the tip of the iceberg but
15 they are not typical of what we see in the community at
16 large and they are not typical of what we see in, say, an
17 average family practice. The people who are in the trials,
18 by definition, have to be relatively clean cases of whatever
19 they are without other co-morbid confounding conditions.
20 They have caregivers who have time and motivation, and who
21 come with them and who bring them year after year for these
22 trials. In my experience, in my opinion most people are not
23 like that. People that I see in the clinic as my patients
24 are not like that, and people we see in our community
25 studies are not like that, and I will try and focus my

1 presentation on that perspective because a lot of the things
2 I was going to say have been said many times already.

3 [Slide]

4 These are the FDA's five questions, which now
5 everybody knows so we don't have to look at them again.

6 [Slide]

7 Since I don't have any answers I thought I would
8 bring some questions of my own. What is this MCI thing we
9 are talking about? How is it different to AAMI? I didn't
10 hear CIND mentioned today so I thought I would throw that
11 in. That is cognitive impairment/no dementia, which I
12 believe was used in the Canadian studies and some others.
13 How is it related to the CDR, which we have all come to know
14 and love? How is it similar or different to normal aging?
15 Is it a single condition? Is it a homogenous condition?

16 My point about heterogeneity is not just what we
17 have heard today already but about the fact that the same
18 person can have many co-morbid conditions, and in real life
19 they do. I see people who probably are in the very early
20 stages of incipient AD but who also drink and are
21 hypothyroid and have black lung disease, and I do not know
22 how much of their cognitive impairment or which part of it
23 to attribute to this condition, but they meet your CDR
24 equals 0.5 criteria or their MCI criteria, and it is not
25 simply that I can take this person out of this box and put

1 them in another one because he seems to belong in many
2 different boxes at the same time.

3 [Slide]

4 So, as clinicians we are quite familiar with these
5 patients who do not seem either quite normal or quite
6 demented, and typically we make a judgment or we reserve a
7 judgment as to whether we think they have an incipient
8 dementing disorder. One question about that judgment is
9 whether we would all make the same judgment. Would Ron
10 Petersen and I or Ranjan Duara and I make the same judgment?
11 I know Steve DeKosky and I don't make the same judgment.
12 And, if not, would neurologists agree, or would reasonable
13 neurologists agree? Would two psychiatrists and
14 neurologists agree? Or, would a family practitioner and a
15 neurologist agree? Would we even see the same patient? For
16 someone to refer a patient with memory disorders to a memory
17 disorder clinic, that person probably has very little else
18 wrong with him. He is not going to be somebody who can't
19 walk and can't breathe because of arthritis and black lung
20 disease. Maybe the arthritis has nothing to do with the
21 memory loss but maybe the hypoxia does. So, we wouldn't be
22 seeing the same patient and we might attribute the causes
23 differently.

24 [Slide]

25 So, we might as well put the blame where it

1 belongs and call these Petersen criteria. This is kind of a
2 straw-man situation that Ron is now in. These are the
3 criteria that we are all quite familiar with but since we
4 have been talking so far about the criteria for MCI, I would
5 like to focus your attention on number five for the moment,
6 which is what do we mean by not demented? We are, as Steve
7 said, victims of our own criteria. We are victims of these
8 dementia criteria.

9 The NINCDS criteria were published in 1984. They
10 say that you cannot have onset of AD after age 90. Well,
11 this is 2001 and I have patients who were perfectly fine
12 until the age of 92. What am I supposed to call them? Are
13 we going to be locked in forever into these criteria that
14 were written, you know, in good faith 20 years ago? We have
15 learned a lot since then. Are we allowed to move the
16 criteria along because it is not just where does normal
17 aging cross over into MCI; it is also when do we say that
18 they are now demented?

19 [Slide]

20 So, here my attempts to answer -- not to answer
21 but to ask further questions about the FDA's questions.
22 What we are really saying is can we take Ron Petersen's
23 criteria and apply them to patients in the clinic?

24 [Slide]

25 What does this mean? Must the patient complain

1 spontaneously of memory loss or can I elicit it by
2 questioning? What if the patient denies memory problems?
3 What if there is no reliable informant? This never happens
4 in your Alzheimer centers but it happens to me all the time.
5 I see people who live by themselves, who say they are
6 absolutely fine; who say that they were at dinner yesterday
7 with somebody who has been dead for ten years but I don't
8 have anybody to contradict that. And, can patients who
9 don't know they have memory loss have MCI by definition?

10 [Slide]

11 The next item is the normal ADLs. How do we
12 decide what normal ADLs and IADLs are? Is this what the
13 person himself or herself says? Is this what the family
14 member says? What if there is no family member? And,
15 doesn't it depend on the demands of your daily ADLs?

16 A situation I run into very often in our community
17 study is that I will see an older couple who live alone.
18 Since the husband retired from the steel mills his ADLs
19 consisted of getting up, getting dressed, watching football
20 and putting away several six-packs of beer. He would have
21 to be pretty impaired for those ADLs to be interfered with.

22 [Laughter]

23 But his wife, who has not retired, who is still
24 cooking and keeping house and cleaning, the first day she
25 forgets to put salt in the spaghetti sauce, everybody is

1 going to notice and say something is wrong. I mean, I
2 understand why people have to have some distress or
3 perceived disability in order for us to say they are
4 diseased, but this makes this definition of functional
5 disability so relative that it is really going to depend on
6 an individual patient's daily life.

7 [Slide]

8 What do we mean by normal general cognitive
9 function? Does this mean normal Mini-Mental State Exam
10 scores? And, let's get real, this is the most that is ever
11 going to be done in family practice. And, what do we mean
12 by normal? Do we mean normal compared to this person, as we
13 have discussed earlier? Does it depend on age, sex
14 education and so on? How does the physician in family
15 practice know whether the person's Mini-Mental score is
16 normal?

17 By the way, I am engaged right now in a study of
18 dementia in primary care, and we sometimes see a notation in
19 the patient's chart that the Mini-Mental State Exam was
20 within normal limits. So, the physician has this idea of
21 what those normal limits are but he hasn't written it down
22 and he is not keeping his medical record primarily for me.
23 He knows what he means by that but I don't, and I don't know
24 if he did a full Mini-Mental. But, clearly, the physicians
25 have some idea of what normal is and that may or may not be

1 a reasonable concept.

2 [Slide]

3 What do we mean by abnormal memory for age? Must
4 everybody be using the same memory test, the Wechsler Memory
5 Scale, as was used at the Mayo Clinic? And, do norms have
6 to be available? Now, I am a fan of "Prairie Home
7 Companion" and so I know that a lot of Ron Petersen's norms
8 are from Norwegian bachelor farmers --

9 [Laughter]

10 -- which would probably not be appropriate age
11 norms in the Monongahela Valley. To be serious, at the
12 other end. One lady comes to mind who was in her early 80s,
13 African-American, had a Ph.D., had been a professor at
14 Pittsburgh. I don't think there are age norms that I could
15 use for her. Really what it boils down to is can we
16 diagnose MCI without neuropsychological testing, without
17 volumetric MRI, without brain biopsy? You know, if we can't
18 do those things are we really going to be able to ask family
19 care practitioners, who are going to see the majority of
20 these patients -- are we seriously going to ask them to
21 diagnose MCI and institute treatment?

22 [Slide]

23 I raved and ranted about this a few minutes
24 already but how is dementia being defined? Does it mean not
25 meeting DSM criteria? Does it mean something on the CDR

1 scale? This ADL component of this is what I am most
2 concerned about. Does it have to interfere with social and
3 occupational functioning before we choose to intervene?
4 And, what do we mean by that in a given case?

5 [Slide]

6 Now for the validity of the clinical criteria,
7 what does validity mean? It means do the criteria in fact
8 measure what they purport to measure?

9 [Slide]

10 Here are some of the aspects of validity which I
11 learned in epidemiology. Yes, they have face validity.
12 They make sense. They appear valid. They appear to cover
13 the appropriate content. But there are also criterion-
14 related validities we have to consider. Concurrent validity
15 is when you know there is an external, independent gold
16 standard criterion at the same time, and predictive validity
17 is when you want to predict something that will happen in
18 the future.

19 [Slide]

20 With face and content validity, I think it seems
21 internally consistent but, again, these questions came up
22 already -- is the amnesic MCI or the Petersen criteria a
23 little too exclusive? Does MCI have to be amnesic? Can
24 another cognitive domain be impaired in isolation?

25 Here is one that I am interested in, can the

1 single domain that is impaired be executive functioning?
2 There is starting to be some data suggesting that this might
3 be one of the first areas in which we see impairment. As a
4 psychiatrist, I see a lot of patients who might have a
5 little memory loss but what they have noticed, the family
6 noticed or what I have noticed is a little bit of a change
7 in personality. They don't quite get it. They don't quite
8 get a joke the way they used to do; a little bit of a loss
9 of abstraction. This may be just a place we didn't look
10 before but we do know that frontal lobe impairments are
11 present early, and could that be an executive MCI? And, how
12 many of us in the room might say we are going there
13 ourselves?

14 [Slide]

15 Concurrent validity -- again, I am restricting
16 myself to Ron Petersen's paper because at least I know we
17 are friends and our friendship will survive this, but in
18 Ron's paper compared to controls, MCI subjects had greater
19 memory loss but were otherwise similar to controls. And,
20 compared to mild AD patients, the MCI cases had similar
21 memory loss but were less impaired in other cognitive
22 domains.

23 [Slide]

24 If that is how you define MCI, how else could it
25 be? If we said that they could be abnormal only in memory,

1 then that is the only way in which they are going to be
2 worse than controls, and the AD patients who don't have that
3 restriction will be worse at everything else or at several
4 other things.

5 [Slide]

6 So, then we are really focused here on predictive
7 validity, and we seem to have decided that the outcome of
8 interest for predictive validity is going to be conversion.
9 In the Mayo Clinic sample it was at the rate of 12 percent a
10 year but I didn't fully understand that because the
11 denominator is not constant. But what do we mean by
12 conversion? Here I am going to quote my friend and
13 colleague Dennis Evans, in Chicago. With no chronic
14 disease, do we really know when onset occurred? The example
15 that Dr. Evans uses is arthritis. He said, "you know, I
16 have some swelling in these joints. I'm not dysfunctional
17 yet. Do I have arthritis? I'm going to get it. The
18 pathology has probably started but do I have it yet?" What
19 is the point at which conversion or the onset occurred? If
20 you see the patient once a year, you might say, yes,
21 something happened in this past year. If you see them once
22 a week you would not be able to pinpoint the week in which
23 it occurred.

24 [Slide]

25 So, it is a gradual process. It reinforces this

1 notion that it is along a continuum. So, are we talking
2 about a change in diagnosis or primarily a change in
3 severity? Going back to the cardiovascular analogy, are we
4 talking about going from mild angina to severe angina? Are
5 we talking about going from angina to myocardial infarction
6 where some structural damages now occur? That may have
7 something to do with how we choose to treat it. Who are the
8 subjects who don't convert? Is it only a matter of time
9 before they all convert, and do some of them convert to
10 conditions other than AD or in addition to AD? You can have
11 more than one thing. You can have vascular damage as well
12 as AD.

13 [Slide]

14 So, is MCI a separate entity? Is it an
15 intermediate stage? Is it always incipient AD? Could it
16 sometimes be something else? We have gone over this already
17 so I will move on.

18 [Slide]

19 Can we distinguish MCI from AD and other causes?
20 It doesn't seem to me that we have a lot of data on other
21 causes, although Dr. Duara started to show some of that and
22 I believe Phil Gorelick will have a lot of good stuff
23 tomorrow, but I won't be here to hear it, on vascular
24 cognitive impairment, or whatever. But this may all just be
25 a function of it being a different stage in the disease or

1 in the same disease as long as we are just talking about
2 people we think have incipient AD.

3 [Slide]

4 So, appropriate outcome measures I think should
5 include both raw and change scores on memory scores, general
6 mental status scores, other cognitive scores. But we should
7 be looking at stability versus improvement versus rate of
8 decline, and we should be looking at conversion, although I
9 have trouble thinking of it as such a categorical event.

10 [Slide]

11 I guess we need to have double-blind, parallel
12 placebo-controlled trials and exclude as few people as
13 possible, have enough people and follow them for long enough
14 and include everybody you intended to treat.

15 [Slide]

16 Some other ideas that came to mind were should we
17 have a normal aging comparison group that is age and sex
18 matched to your MCI cases and is not on drug? Of course,
19 you would be talking about following them over a very long
20 period of time just so we don't lose sight of how much is
21 normal aging on the same measures. I think the source of
22 the MCI subjects is extremely important. We may really need
23 to do effectiveness studies before we can say we know what
24 is going on because the patients in primary care are not the
25 patients in your Alzheimer center.

1 [Slide]

2 That is my final slide. The epidemiologist in me
3 is creeping out. I think we don't know the epidemiology of
4 this condition. We don't know how it is distributed in the
5 population at large. There may be lots of people who meet
6 the criteria who just never come forward and complain. I
7 don't remember as well as I used to, you know, and I
8 certainly don't remember as much as a young child or learn
9 as fast as a young child does, but I think it would be
10 important to have some sense of how this condition, whatever
11 it is, is distributed and what is associated with it, and
12 who the people are before we do the definitive trials.
13 Thank you.

14 DR. KAWAS:

15 DR. KAWAS: Thank you, Mary, for your pragmatic
16 approach from the trenches. The floor is now open for
17 questions.

18 DR. DUARA: Mary, I would go back to my previous
19 question, which is why are we looking at conversion rates
20 when what I gleaned from what you said is that there is a
21 lot of variability. It depends on who you are asking about
22 a particular person whether they are demented or not, what
23 the informant tells you about how they perform their ADLs,
24 whether the informant is interested or not. There are so
25 many different variables, why would we want to enter all

1 those possible variable answers into a statement about
2 whether this person has converted, so to speak, from one
3 state to the other, and everything that we have seems to
4 suggest that it is just a continuum? Why draw this
5 artificial line in the sand?

6 DR. GANGULI: Well, I share your view about the
7 continuum, and my understanding of why we are discussing
8 this conversion is only to try and find out an appropriate
9 endpoint for an MCI trial. My view as a clinician is that I
10 can already treat somebody off-label if I think that he has
11 incipient AD. I don't really need to have the FDA or DSM
12 say that MCI is a non-indication. So, we are really talking
13 about defining a prodromal situation perhaps. But then I am
14 already saying that we are restricting ourselves to the MCIs
15 who are prodromal AD.

16 So, if the question is how do we better define
17 this condition for its own sake so we understand the
18 pathology, that is one thing. If you are saying how do we
19 define it as an indication for drugs, that is a question I
20 am not qualified to answer.

21 DR. KAWAS: Dr. Petersen?

22 DR. PETERSEN: As we were saying earlier, I think
23 there is some validity in defining a concept and being
24 relatively strict with regard to the criteria, especially if
25 they do follow a pattern. So, there is no doubt that there

1 is heterogeneity in the concept but I think as a subset of
2 these people are defined as having an amnesic variety, the
3 prodromal Alzheimer's disease variety, there is much more
4 consistency among the criteria, reliability among people,
5 and progression of these individuals than in the more
6 heterogeneous group. So, I think that research down the
7 road may, in fact, find prodromal states for Lewy body
8 dementia or frontal temporal dementia, and the like, and
9 that is a worthy target. But for this purpose, I think if
10 we confine it to a discussion of what might be prodromal AD
11 it is going to be more beneficial.

12 The other issue that you brought up was the reason
13 that we have always retreated to using these criteria in a
14 clinical sense is just as you have highlighted. You have to
15 take the information from the informant as well as it comes.
16 It may be reliable; it may not be. You take the same
17 information from the patient him or herself. I would like
18 to augment that with neuropsychological testing but I am not
19 bound to it. So, if you have the Ph.D. physics professor
20 who has noted a change in his or her cognition but when you
21 test them are still scoring well above the mean but you
22 infer that this is a change for this person, then you take
23 that into account and that then becomes clinically relevant
24 that this person has, in fact, experienced a decline.

25 So, I think where we get into trouble and where we

1 get into trouble in the literature is when we take the
2 criteria too literally, and when somebody describes their
3 clinical population saying, on the average, the memory
4 function is about 1.5 standard deviation below the normative
5 data -- that is on the average. Some may be more; some may
6 be less and it is up to the clinician to make that judgment
7 but I think if you put some restrictions around the criteria
8 you can get some agreement among different people.

9 DR. FERRIS: I liked your presentation very much
10 and I think it really helps to have a real-world
11 perspective. Just a brief comment on the acronym you
12 referred to that hadn't been previously mentioned, CIND. My
13 understanding of CIND is that it is extremely broad in its
14 definition, such that it doesn't even require that there be
15 an age-associated underlying cause. It could be anything
16 that causes mild cognitive impairment. Then, of course,
17 they have the subgroups that are very MCI like in the sense
18 of how we have been discussing it today. So, I think the
19 data from those longitudinal studies are extremely useful
20 but they have to be looked at very carefully because I think
21 you really have to narrow the look of that data to the
22 subgroups that are more like the age-associated pre-dementia
23 syndrome that we have been talking about today.

24 DR. GANGULI: I agree.

25 DR. PETERSEN: The Canadian study of health and

1 aging coined this term, CIND, and as the term implies, it is
2 very broad and, as Steve said, it does not necessarily imply
3 a change and includes things like static encephalopathies.
4 But the researchers are now taking and subdividing that
5 group to see if there is a subclassification that coincides
6 with MCI.

7 DR. GORELICK: Phil Gorelick, Chicago. Mary, the
8 epidemiologist crept into you at the beginning of your
9 presentation when you said it might not be cost effective to
10 treat these patients. What I haven't heard so far, unless I
11 have missed it, is what is the magnitude of the public
12 health problem of MCI. Do you know that or do some of the
13 other panelists know that?

14 DR. GANGULI: I don't know.

15 DR. PETERSEN: I can just say, and maybe Mike can
16 expand on some of this, it is hard to project the, say,
17 prevalence figures for MCI with the variations in
18 definition. On the other hand, if you take the theoretical
19 assumption that all people who develop Alzheimer's disease
20 go through some kind of transitional stage, namely an MCI
21 kind of a condition, then you can infer that there must be
22 at least as many MCI people out there as there are
23 Alzheimer's disease at some point in time. Mike, you have
24 done some extrapolation figures?

25 DR. KAWAS: Dr. Grundman next and then Dr. Duara

1 and then Dr. Ferris.

2 DR. GRUNDMAN: I can just say we did some sort of
3 back calculations based on the expected conversion rate to
4 AD in MCI patients, looking at the prevalence of elderly
5 people in the United States and we came up with a figure of
6 about 2.5 million just based on theoretical projections.

7 DR. DUARA: In an attempt to answer Phil
8 Gorelick's question, if you look at the screening survey
9 that we did, and we have screened now about 6000 people over
10 the last 10-12 years -- and this is obviously not
11 representative of the general population, these are people
12 who have come in because they think they have a problem, or
13 they may have a family history or something like that, but
14 if you look at the distribution there, based on the kind of
15 scores that I showed you, the cut-offs, the people whom we
16 would consider normal or "worried well" who score well above
17 the threshold in everything constitute 65 percent of the
18 group; 30 percent of the group are what we would call MCI;
19 and 5 percent meet criteria for dementia according to those
20 numbers.

21 DR. KAWAS: Dr. Duara, how do you extrapolate
22 those figures to the population to get an estimate?

23 DR. DUARA: Well, it is not possible. I am just
24 giving you an example of a survey that we did to tell you
25 what the general distribution was.

1 DR. KAWAS: And, that was 30 percent for MCI.
2 What was the denominator? Just people who came to clinic?

3 DR. DUARA: That is right, who responded to an
4 advertisement and came because they thought there may be a
5 problem or they were concerned about their family history,
6 or something like that.

7 DR. FERRIS: With respect to the prevalence of MCI
8 of the Alzheimer type, there is very nice sort of
9 statistical modeling that Jerry Savage and Helena Kramer and
10 that group has done. I actually have a slide illustrating
11 it but I didn't show it because there is a possibility it
12 will be shown this afternoon. But it is possible to sort of
13 back-calculate from the published data on annual incidence
14 of Alzheimer's disease, and if you make the assumption that
15 there is a certain conversion rate from MCI to AD for each
16 of those incident cases of AD you end up with age-specific
17 prevalence rates of AD of the MCI type that are as large or
18 larger than the age-specific indices rates of AD because
19 that is the feeder group crossing the AD threshold. That
20 data is I think going to be published. It was presented at
21 a meeting in Europe. It is a very nice statistical modeling
22 but it is not real data.

23 DR. REISBERG: We have long been able to estimate
24 the duration of MCI. This goes back many years. One is
25 able to do this using various procedures. One is

1 prospective studies on time to conversion when people are
2 coming in. They are usually coming in actually with these
3 symptoms midway or even a little bit past midway. They
4 convert in about two to three years. You can also project
5 backwards utilizing neuropathologic data and a few different
6 conversion means looking at this. Another way to do it,
7 which is the way we started to do this, was clinically to
8 take the earlier symptoms to see how long it takes the
9 patients to convert. Using those three different approaches
10 we have estimated that the MCI stage is approximately seven
11 years, which would be a big chunk of the total duration of
12 Alzheimer's disease. Actually, the numbers that one gets
13 from this are very close to the numbers that Michael was
14 giving us before.

15 DR. KAWAS: Dr. DeKosky, and then we will move on.

16 DR. DEKOSKY: I think the answer that your group
17 is looking for comes from the population epidemiologic
18 studies, not the community-based studies. So, as I study at
19 the feet of my epidemiology instructor, Dr. Ganguli, we have
20 been looking in the CHS study at the numbers of people who
21 have MCI at any one point and then their progression. We
22 don't have the percentage yet. It is clear that you can
23 identify these people in the population studies. The first
24 impression I have is that we have fewer of what we would
25 characterize as the pure amnesic MCI cases than we do the

1 other, less well-defined cases but, of course, there is also
2 a great deal of vascular pathology in that group that
3 probably, we think, has an effect on this which, for the
4 most part, we don't see when we bring our patients into the
5 clinic whom we diagnose with amnesic MCI.

6 So, as more and more of the add-on studies to some
7 of the other longitudinal studies are done, I think we will
8 define various levels of cognitive impairment both in the
9 prevention trials and, as people go back into their data
10 from epidemiological studies we will define, I think, what
11 the approximate load is of people with this specific kind of
12 cognitive impairment and the more generalized kinds. But,
13 oddly enough, we actually don't have that yet from many of
14 the U.S. studies.

15 DR. KAWAS: I think that is a very important
16 point. I mean, essentially it is saying that what we need
17 to do to find the estimate that people are looking for is to
18 go back to the trenches. Extrapolating from all these
19 clinic samples certainly is going to be fraught with
20 problems. Even though I am not an epidemiologist, I can
21 tell that.

22 We have one more speaker that we are going to try
23 and fit in before lunch, but we have an announcement that
24 Dr. Titus is going to make.

25 DR. TITUS: We have been informed by the hotel

1 that the fire department in the county wants to have a fire
2 drill at this hotel today. Consequently, we don't have much
3 to say about it, but we believe that the fire drill is going
4 to occur sometime after 12:30, which means that none of you
5 has to go outside. Where you don't want to be is up in your
6 rooms because I think they are going to do room searches
7 because that is what they are concerned about. So, if it
8 happens during this next block of time before we finish, I
9 think we are probably going to try to sit out the alarms.
10 If it happens during lunch, I have been assured that you can
11 eat lunch. So, I don't think it matters at all, except if
12 you go to your rooms.

13 DR. KAWAS: Thank you. Our last speaker before
14 lunch is Dr. Michael Grundman, from the University of
15 California at San Diego. Dr. Grundman's title is clinical
16 trial designs for MCI.

17 Clinical Trial Designs for MCI

18 DR. GRUNDMAN: Thank you.

19 [Slide]

20 About five years ago about 17 Alzheimer's disease
21 centers got together and pooled data on approximately 1200
22 normals and 700 MCI subjects. What was found was that the
23 normals progressed at a rate of approximately one percent
24 per year, while those with mild cognitive impairment
25 progressed at a rate of approximately 15 percent per year.

1 [Slide]

2 More recently we have come back and we have done a
3 totally new data collection among 16 centers, involving
4 almost 5000 people, 4000 normals and approximately 900 MCI
5 patients. What we find here is that memory testing clearly
6 increases the prediction accuracy of Alzheimer's disease
7 over the clinical evaluation alone. Not to say that
8 clinicians are not very good at predicting when there is an
9 increased risk of Alzheimer's disease, but when you combine
10 it with cognitive testing it is clearly better. This is
11 true not only of people who have symptoms of memory loss,
12 which you can see in the second two graphs, but it is also
13 true of people who are normal so that people who have
14 cognitive impairment while they are still normal are at
15 higher risk of developing AD.

16 [Slide]

17 So, what are we really all talking about here?
18 What we are really talking about is trying to develop
19 clinical trials to prevent AD, which is obviously an
20 important public health goal. Primary prevention trials are
21 one way of doing this. That is, they recruit a lot of
22 normal people and then follow them clinically. If you want
23 to put them in a trial you give them a drug, and then wait
24 until they develop AD.

25 But, as I mentioned before, the rate of conversion

1 is very low in normal people. So, this requires thousands
2 of subjects to be enrolled in the trial. There are
3 relatively few conversions to AD or dementia. It requires a
4 very long period of follow-up, and if you try and enrich on
5 the basis of, for example, recruiting only very old
6 individuals who have a higher conversion rate to AD your
7 trial results may be only limited to people who are very
8 old. Obviously, people who have sort of mild cognitive
9 impairments that we have been talking about wouldn't be able
10 to participate in those trials. Also, the conclusions that
11 you can draw from those trials are very important but also
12 bear in mind that a lot of the patients that enter those
13 trials will never finish them because they will probably die
14 before they are over.

15 The other point, which I showed on the previous
16 slide, is that even if you do a primary prevention trial a
17 lot of the people who are at the highest risk for developing
18 AD actually have some memory impairment on cognitive testing
19 when they enter the trial.

20 [Slide]

21 This graph shows dramatically how an MCI study is
22 much more manageable than a primary prevention trial. If
23 the conversion rate is between 3 and 12 percent in terms of
24 your final outcome measure, conversion to AD, then you are
25 going to need somewhere between 2500 and 10,000 subjects.

1 On the other hand, if you have a conversion rate which is
2 somewhere between 30 percent and 45 percent, you can do a
3 clinical trial looking at prevention of Alzheimer's disease
4 with several hundred subjects, which is actually manageable
5 and a lot less expensive.

6 [Slide]

7 Just to summarize that, in an MCI AD prevention
8 paradigm there is a higher proportion of people who are
9 likely to develop clinical AD over the course of the trial.
10 You require fewer subjects. Younger people can participate.
11 It is less costly. It has a shorter duration. Finally,
12 with all the different treatments that are being tested, it
13 is not really going to be practical to try to do primary
14 prevention with all of those types of agents. You are going
15 to need to have some sort of a bridging methodology to try
16 to determine which preventive agents are going to be most
17 effective and this is the population that we have that we
18 can do it in.

19 [Slide]

20 One example of an MCI trial that we are currently
21 doing has three treatments, vitamin E, Deprenyl and placebo.
22 The goal of the study is to prevent the development of
23 Alzheimer's disease, show some decline on measures of
24 cognition and activities of daily living, reduce rate of
25 atrophy on MRI in a subset of patients. The trial has a

1 three-year duration with approximately 760 participants, and
2 we are conducting it at 75 centers.

3 [Slide]

4 The criteria for selection are those that Dr.
5 Petersen has pointed out earlier, namely, that patients that
6 enroll in the study have to have memory complaints that can
7 be verified by others. They have to have a memory
8 impairment documented with a cognitive instrument. Their
9 general cognition and function must be preserved such that a
10 clinician would not diagnose Alzheimer's disease. The Mini-
11 Mental has to be greater than 24, a clinical dementia rating
12 scale of 0.5, Hachinski score of less than or equal to 4. A
13 spouse or companion available to spend several hours a week
14 with the patient; no evidence of an underlying neurologic
15 disease on baseline imaging; no clinically important
16 laboratory abnormalities; and no concomitant use of
17 medications that might impair cognition.

18 [Slide]

19 The primary trial endpoints are conversion to AD.
20 In addition to the face validity that I mentioned earlier,
21 another reason for this is because we know the natural
22 history so we can predict what we might expect in a clinical
23 trial, which is really critical and which is another reason
24 why the measures of cognitive impairment at entry into the
25 trial are important because if we do a trial and we can't

1 predict how many people are going to develop the outcome at
2 the end of the trial, then if we are surprised and we only
3 have a five percent conversion rate and we enroll 760
4 patients, we are never going to be able to show a treatment
5 difference. So, it is important to have some idea of what
6 the percentage of endpoints are going to be at the end of
7 the trial.

8 Also, there have been numerous studies which have
9 shown that the diagnosis of AD based on NINCDS criteria have
10 a very high inter-rater reliability as you can see from this
11 current setting, higher than the consensus about what MCI
12 reliability is right now.

13 So, the cognitive measures that we are looking at
14 include general measures including ADAS-COG and Mini-Mental.
15 In addition, we have a neuropsychological battery which taps
16 into memory, attention, visual-spatial, language domains.
17 There are clinical and functional measures that we are
18 looking at, including the Clinical Dementia Rating Scale;
19 the sum of boxes on the Clinical Dementia Rating Scale; a
20 global measure that the clinical carries out called ADCS-
21 CGIC. We also have an activities of daily living scale
22 especially designed for MCI patients, and the global
23 deterioration scale as secondary measures. Also, in a
24 subset of patients we are looking at neuroimaging and
25 oxidative markers to try to get at the issue of whether or

1 not there is disease progression as opposed to only clinical
2 progression.

3 [Slide]

4 The characteristics of the patients who are
5 enrolled in this trial -- you can see here in the second
6 column. They have a Mini-Mental of 27; and ADAS-COG score
7 at baseline of 11, which is very different than the patients
8 that have typically been enrolled in AD trials until now
9 where the average mean Mini-Mental tends to be about 20 and
10 26 for the ADAS-COG. Notice that they are closer to normal
11 on these general measures of cognitive and, in fact, some of
12 the decrement that you see on the general measures is
13 probably related to the fact that they have memory deficits
14 and these general measures include memory items.

15 On measures which specifically look at memory, you
16 can see that they have impairment compared to normals, not
17 quite as bad as those that you would typically see in mild
18 AD patients. Their ADL scores are close to normal, and they
19 sort of fit towards the lower end of the spectrum on
20 activities of CDR sum of boxes compared to patients in mild
21 or moderate AD trials.

22 [Slide]

23 These are the MCI patients enrolled in our trials.
24 You can see that they have, compared to mild AD patients,
25 fairly mild or subtle impairments on the CDR domains such as

1 judgment, hobbies, community, personal care. Memory seems
2 to be the highest complaint, and these other areas are very
3 slightly impaired compared to AD patients where there is
4 clear evidence that they are impaired in these domains.

5 [Slide]

6 In addition, from baseline data that we have so
7 far there appears to be a clinical correlation between the
8 memory performance obtained at baseline and the hippocampal
9 volume, suggesting that possibly as a secondary outcome
10 measure as time goes on we may be able to see, if there is a
11 change on cognition, whether or not there is also a change
12 in hippocampal volume as a measure of disease progression.

13 [Slide]

14 So far, the conversion rate to Alzheimer's disease
15 in the trial appears to approximate that which we predicted
16 would occur based on our preliminary data, namely about 15-
17 16 percent per year.

18 [Slide]

19 This is the rate of progression so far over the
20 course of one year that we have in a subset of about 250
21 patients. You can see very clearly that in standard AD
22 trials the types of movement that you see on the Mini-Mental
23 and ADAS-COG are much greater than you see in patients with
24 mild cognitive impairment. So, as a group they are showing
25 very slow movement, which is another reason that it might be

1 hard to try to power your study based on these cognitive
2 tests.

3 Interestingly, the global impression of change --
4 there is some evidence of subtle worsening in a fair
5 proportion of patients with mild cognitive impairment, but
6 they still don't meet criteria for AD according to the
7 doctors who are seeing them at the sites. They have also
8 some slight worsening on their CDR sum of boxes.

9 [Slide]

10 As I mentioned, the blue bar is a measure of what
11 all the MCI patients are doing as a whole, and you can see
12 that in general they haven't changed much from the baseline
13 over the course of the year. While in the people who are
14 converting to AD there is evidence that they are declining
15 more rapidly on global, cognitive and ADL measures.

16 [Slide]

17 The conclusions that we can draw from this are
18 that, first of all, we thought we could identify MCI
19 patients for a clinical trial and it looks like we have
20 actually been able to do it according to what we predicted.
21 They have a decline in memory beyond that expected with
22 normal aging. Compared to patients diagnosed with AD, they
23 have less impairment on their cognitive and functional
24 measures. They decline more slowly than patients with AD,
25 and they seem to be at increased risk of developing AD.

1 It is pretty clear that this population, based on
2 the results of clinical and ADAS-COG data from clinical
3 trials, from standard, conventional AD trials, that it would
4 be unreasonable, I think, to extrapolate recommendations
5 based on those trials with the endpoints that they used to
6 patients with MCI. So, indeed, I think MCI trials do
7 require different trial designs and I think it provides an
8 important opportunity for us to both look at drugs that
9 might improve memory loss and prevent further decline to AD.

10 [Slide]

11 It looks like MCI trials are likely to meet their
12 goals of demonstrating whether or not an agent can reduce
13 the risk of developing clinical AD. Short-term MCI trials
14 may work if they are particularly effective at reversing
15 pathology or improving symptoms of cognitive impairment.
16 And, biological markers would obviously be very helpful
17 short term as well as long term in trying to determine
18 whether or not the clinical measures are moving as a result
19 of some effect on the underlying disease process.

20 [Slide]

21 Finally, I just wanted to comment on the value of
22 a mild cognitive impairment diagnosis. I think that
23 dementia, which is almost synonymous with Alzheimer's
24 disease, is understood to refer to a generalized loss of
25 intellectual abilities with disturbed behavior. I think

1 there are many people out there who don't fit into a nice,
2 neat category of black and white, normal versus dementia.
3 There obviously is a transition zone where clinicians are
4 just not quite sure what to call these people and I think,
5 rather than calling them demented, it would make more sense
6 to call them mildly cognitively impaired. It is a more
7 accurate description of their clinical status and it is more
8 acceptable to patients at this stage of their illness. It
9 also reflects the uncertainty about when the transition to
10 AD and dementia will occur for patients, although clearly
11 the diagnosis implies an increased risk.

12 I think that if the goal here is to try to get to
13 prevention, then we need to get the patients into the clinic
14 where we can give them a diagnosis that is going to be less
15 stigmatizing than AD so that they will get earlier
16 treatments.

17 DR. KAWAS: Thank you, Dr. Grundman. The floor is
18 open for questions. We will start with Dr. Gerald Van
19 Belle.

20 DR. VAN BELLE: Michael, just a few questions on
21 the trial. What are the primary endpoints? I know that
22 conversion to AD is one of them, but what are all the
23 others? You have about 15 of them. Are there ones that are
24 more important than others?

25 DR. GRUNDMAN: The primary one is conversion to

1 Alzheimer's disease. The other ones are all secondary. So,
2 the primary endpoint is going to be whether or not we can
3 show a reduction in the rate of conversion to Alzheimer's
4 disease.

5 DR. VAN BELLE: One more question, how long do you
6 expect to follow these patients up? I notice that the trial
7 is three years. So, how long will the average follow-up
8 time be?

9 DR. GRUNDMAN: How long will the average be?
10 Three years. I mean, ideally we would like to follow all
11 the patients out to three years, with the goal being that,
12 you know, we are powered to detect about a one-third
13 reduction in the rate of conversion. So, you know, if we
14 expect a 45 percent conversion at the end of three years in
15 the placebo groups, then in the active groups we might
16 expect, if the drugs work, to have a 30 percent conversion.

17 DR. VAN BELLE: Just to make sure, the study won't
18 actually last longer than three years?

19 DR. GRUNDMAN: The study will last three years.
20 You are saying what is the expected period. We are going to
21 follow all the patients even after they convert till three
22 years. You are saying that the average time that we are
23 going to be following them is going to be less than three
24 years? Is that what you are saying?

25 DR. VAN BELLE: I am talking about funding.

1 DR. KAWAS: Five years.

2 DR. VAN BELLE: Thank you.

3 DR. FERRIS: Three years from the entry of the
4 last enrollee.

5 DR. PENIX: Was there a correlation between your
6 functional outcomes and the rate of conversion of patients
7 to AD?

8 DR. GRUNDMAN: We haven't looked at that yet, not
9 in this trial, no. I mean, others have looked at that and
10 obviously there is a close correlation between functional
11 measures and development of AD.

12 DR. WOLINSKY: I am just curious in terms of your
13 thoughts about trial design for something like this. Do you
14 have built-in interval analyses for efficacy and futility?

15 DR. GRUNDMAN: Yes. After two-thirds of the
16 endpoints are collected we are planning to do an interim
17 analysis.

18 DR. KAWAS: Actually, I have a question. Mike,
19 you mentioned at the end how unreasonable it was to
20 extrapolate from patients with Alzheimer's disease to this
21 group. But at the beginning and throughout much of the talk
22 you implied that it was reasonable to extrapolate from these
23 people to primary prevention. I have trouble with this
24 model. I mean, I can understand how TPA might work once the
25 symptoms start but it wouldn't be something that we would

1 give to people chronically for primary prevention where we
2 have a completely different approach. Are you sure that it
3 is reasonable for us to find primary prevention modalities
4 out of this study in MCI?

5 DR. GRUNDMAN: Well, I think there is sort of a
6 leap of faith and obviously I think primary prevention
7 studies should be done. If we really thought we had a drug
8 that would influence the course of the disease and was very,
9 very safe to give to people who are elderly, that had no
10 side effects, but in this population you have a symptomatic
11 group that we know is going to develop Alzheimer's disease
12 and I think it is reasonable to talk about prevention of the
13 endpoint in this study, which is Alzheimer's disease.

14 DR. PETERSEN: If I could just expand on that a
15 little bit, I think the extrapolation back, if you will,
16 from what Mike is talking about would be to those people in
17 the normal segment of the population who are at risk for
18 developing Alzheimer's disease because of genotype, family
19 history, cognitive function, whatever. So, the problem with
20 what you are saying is right, that you can't extrapolate
21 this back to the whole population because this is not a
22 model of aging. So, not everybody in the population is
23 going to go down this continuum, presumably, but a subset
24 will and that subset, to be defined yet, is the subset of
25 risk. So, I think you could extrapolate it back to that

1 segment of the primary prevention.

2 DR. KAWAS: Let me make sure I understand because
3 I have a lot of trouble with this concept. You are saying
4 that if this trial is positive and shows that MCI people who
5 are treated with one of these agents develops full-fledged
6 dementia later than placebo groups, that would suggest that
7 we should be using these treatments in people with a family
8 history of Alzheimer's disease, and at what point?

9 DR. PETERSEN: No, I don't think I would
10 necessarily conclude that but I think the concept would be
11 that we can prevent or slow down the progression of these
12 symptoms, so where we need to move now is back into the
13 normal population -- maybe not with these drugs. Like the
14 discussion we had earlier, it is not necessarily the case
15 that drugs that might be effective when the symptoms have
16 manifested will be effective as prophylactic therapies, or
17 vice versa.

18 DR. KAWAS: In my mind, we are using this as a
19 model for two things, neither of which works for me. I
20 mean, the assumption that if it works in a group of people
21 who are already symptomatic that it will work in anybody, no
22 matter what the risks factors are, before any symptoms have
23 appeared bothers me quite a bit.

24 DR. GRUNDMAN: We are not saying that. You know,
25 if a drug, say, works in an MCI population I wouldn't think

1 that would necessarily make this a candidate for, say, a
2 smart drug, a drug that could be used by the general
3 population to boost their cognition.

4 DR. KAWAS: Would it be a candidate for a drug
5 that could be put into the general population for primary
6 prevention? I guess that is my question.

7 DR. PETERSEN: It might be a candidate in the
8 subset of the general population who is at risk, and that
9 all has to be worked out but, say, you came up with a
10 susceptibility polymorphism profile that these people who
11 had this profile had really an increased risk of developing
12 Alzheimer's disease 15, 20 years down the road but they are
13 asymptomatic right now, if the putative mechanism of action
14 of this drug -- and this gets back to symptomatic and
15 disease progression -- if you had a compound that were
16 effective on disease progression, I would think that would
17 be a candidate for intervention. However, if it is a
18 symptomatic drug, that will remain to be seen.

19 DR. GRUNDMAN: Claudia, I was just going to say
20 that I think what this does is it opens up the possibility
21 for taking drugs that we think might be useful for
22 prevention in this sort of early detection population, and
23 then have at least some consideration for doing a trial with
24 primary prevention where the resources, both financially and
25 time-wise are so much greater.

1 DR. KAWAS: I guess that is my problem. I mean,
2 first you are saying it could be an efficient way to get at
3 the problem, but it also could be an efficient way to close
4 down the problem. I mean, if this study is negative, does
5 that mean that we now know that those agents are not good
6 for primary prevention?

7 DR. GRUNDMAN: No. But, on the other hand, you
8 have to pick the agents that you think are going to work.

9 DR. KAWAS: Work when?

10 DR. GRUNDMAN: You can't study, you know, so many
11 drugs.

12 DR. DEKOSKY: Claudia, we are ignoring the issue
13 of why we would try medications. So, let's take Ron's case
14 of a susceptibility profile of a series of polymorphisms,
15 who you know has already developed perhaps very early
16 amyloid deposition but no significant fibrillization, no
17 inflammatory component, to give those people an anti-
18 inflammatory medication would not make as much sense
19 necessarily as giving them a medication that tried to block
20 amyloid formation.

21 I think the struggle of the day is that in the
22 absence of any evidence that cholinesterase inhibitors delay
23 progression of the pathology, speculations about their
24 effects upon amyloid notwithstanding, we are still all
25 looking at a symptomatic effect. The vitamin E effect would

1 be a much more generalizable one. It is one that you could
2 hypothesize would have an effect in delaying the entry into
3 by slowing down or suppressing the oxidative stress aspects
4 of the very early stages of the disorder and still be
5 effective at least part way into the disease. So, I think
6 the prediction of whether you expected a medication to work
7 both in the pre-state and in the descent state of the
8 disease has to consider what you expect the pathological or
9 the biological intervention to be.

10 I wanted to ask Mike one very quick question.

11 Mike, what is this trial going to cost?

12 DR. GRUNDMAN: This trial will cost 22 million
13 dollars.

14 DR. DEKOSKY: And my only comment is, although I
15 have in my slide very similar pictures that say MCI trials
16 are cheaper to do than primary prevention trials, the GINKGO
17 trial of 3000 people for 5.5 years is targeted right around
18 20 million dollars as well. So, I don't know how much
19 savings there is, although I agree they have very different
20 outcomes and purposes, and will demonstrate different things
21 in the population and I am a little depressed to see that we
22 can't do it for less money than the primary prevention
23 trials.

24 DR. GRUNDMAN: Maybe we will get better. I think
25 we have a lot of testing going on here because this is our

1 first trial and we don't really know what the best outcome
2 measures are going to be. So, I think there may be some
3 ways we could trim down the cost as time goes on.

4 DR. FERRIS: The follow-up on the issue of why you
5 would do a trial of the sort Mike just described, I think
6 there are two basic reasons because, first of all, we
7 shouldn't get away from the fact that we want to find out if
8 a treatment is effective in MCI because MCI itself is a
9 group that is worthy of treating, as we have been sort of
10 ruminating on all morning.

11 On the other hand, it can provide a kind of proof
12 of concept trial, hopefully more cheaply than a large
13 primary prevention trial, such that if you see a positive
14 signal and you are able to interpret that signal as implying
15 an effect on disease course, it provides a rationale for
16 potentially investing in a larger, presumably more expensive
17 primary prevention trial. I think it serves potentially
18 both of those purposes.

19 On the other hand, it is quite true, as has been
20 mentioned, that a negative result doesn't necessarily rule
21 out the fact that a treatment wouldn't work in prevention,
22 but at least it provides some basis for decision-making on
23 the part of sponsors who may be reluctant to launch a large
24 prevention trial.

25 DR. KAWAS: Any other comments? Dr. Duara?

1 DR. DUARA: So far we have focused our discussions
2 on treatment of MCI, the type of MCI that we think is going
3 to be Alzheimer's disease. But several of us have discussed
4 the fact that if you look at the general community maybe 30
5 or 40 percent of patients that you see who meet criteria for
6 MCI don't have, or we don't think have the beginnings of
7 Alzheimer's disease; they have other pathologies going on.
8 The question I am trying to raise is, is it worthwhile
9 discussing treating MCI as a symptom complex regardless of
10 the pathology underlying the symptom? Is it worthwhile
11 thinking about common treatments? Because we already seem
12 to have some data that suggests that, for instance,
13 cholinesterase inhibitors help patients with multiple
14 sclerosis who have cognitive impairment, and there is some
15 data that patients with multi-infarct dementia also seem to
16 respond to cholinesterase inhibitors, in some cases
17 apparently better than Alzheimer's disease patients have
18 responded.

19 So, I think it is worthwhile to broaden this
20 discussion to some extent to discuss this entity of MCI as a
21 symptom complex which is not necessarily just Alzheimer's
22 disease, and whether various drugs that we are using may be
23 used just for the symptom complex.

24 DR. KAWAS: I think that is a very good point and
25 a topic for this afternoon's discussion, and we will make

1 sure that we talk about the whole concept of this as a
2 system complex, independent of disease process. Unless
3 there are any other comments or statements people want to
4 make before we adjourn for lunch -- the speakers and
5 committee members do have a table reserved for them in the
6 restaurant. We will have a lunch break that, barring a fire
7 drill, will last until 1:30 or until they let you back in
8 the building.

9 [Whereupon, at 12:30 p.m., the proceedings were
10 recessed for lunch, to be resumed at 1:40 p.m.]

1 [Slide]

2 As I have already noted, the IPA is concerned with
3 issues such as mild cognitive impairment, and one indication
4 of that concern is that we have organized a symposium
5 concerning some of the same topics which we have been
6 addressing here today at the IPA's next congress, under the
7 auspices of the Pharmacy and Therapeutics Committee, and our
8 next congress will be held in Nice this summer.

9 Let me say that although I am here today as a
10 representative of IPA, and although the IPA is concerned
11 about the issues which I will be discussing, the views which
12 I will be expressing are my own.

13 [Slide]

14 I am going to be speaking about mild cognitive
15 impairment, a broad perspective.

16 [Slide]

17 A number of recent reviews -- shown here is a
18 quote from the review of Sherwin in the Journal of the
19 American Geriatric Society, in the year 2000, which noted
20 that the MCI diagnostic classification was first used
21 systematically based upon a score of 3 on the Global
22 Deterioration Scale.

23 [Slide]

24 Other consensus with respect to MCI have appeared
25 in the past year. Shown here is a very broad international

1 consensus.

2 [Slide]

3 This broad consensus has also noted that the term
4 MCI was first used in the description of GDS stage 3. This
5 usage goes back to the 1980s. Consequently, studies of MCI
6 from this perspective have been conducted for many years,
7 and I would like to share a little about what has been
8 learned in addressing the questions which have been posed
9 here today.

10 [Slide]

11 We have heard here today both about the CDR Scale
12 and about the Global Deterioration Scale, and I would like
13 to spend just a moment translating some of these measures in
14 interpreting the data which I am going to be describing in
15 just a moment.

16 The GDS identifies four stages corresponding to a
17 CDR scale stages of 0 and 0.5. Utilizing functioning and
18 self-care descriptors, one can translate these two measures
19 one to the other. Basically, the GDS identifies two stages
20 corresponding to a CDR stage of 0. These are stage 1.
21 These individuals are elderly individuals who are free of
22 both subjective complaints of cognitive impairment and also
23 free of objective evidence of cognitive impairment. That is
24 GDS stage 1. GDS stage 2 individuals have subjective
25 complaints of impairment only, but those subjective

1 complaints are not clinically manifest.

2 Now, corresponding to a CDR stage of 0.5, the GDS
3 identifies two stages. The first is a GDS 3 stage, and this
4 is a stage in which deficits appear which are subtle in the
5 context of a detailed clinical interview. Functionally, in
6 this GDS 3 stage, individuals have deficits in what are
7 known as executive functions. These are complex
8 occupational and social tasks. Then, the GDS also
9 identifies a GDS 4 stage when deficits become readily
10 manifest in the course of a clinical interview and,
11 functionally, in this stage, individuals have difficulties
12 with what are known as instrumental activities of daily
13 life. These are the complex activities of daily life. They
14 include complex marketing skills; complex meal preparation
15 skills and the management of personal finances.

16 [Slide]

17 Longitudinal studies have determined the meaning
18 of these different stages. Shown here is a longitudinal
19 study published by Kluger and associates in 1999, and this
20 is a study of 213 individuals who were followed over a four-
21 year mean interval in these stages of interest, DGS stages
22 1, 2 and 3.

23 Shown here is the percentage of subjects
24 converting to dementia. None of the elderly stage 1
25 subjects converted to dementia over the four-year interval.

1 Approximately 10-15 percent of the stage 2 individuals
2 converted to a diagnosis of dementia, in almost all cases
3 Alzheimer's disease, over the subsequent three- to four-year
4 interval. In contrast, for stage 3 individuals, the
5 individuals whom we called MCI, a big chunk of these
6 individuals, actually two-thirds in this study, converted to
7 dementia over that four-year interval.

8 Now, other longitudinal studies have shown that
9 individuals from stage 4 onwards show the characteristic
10 course of Alzheimer's disease and, consequently, one can
11 reliably make the diagnosis of Alzheimer's disease from
12 stage 4 onwards.

13 [Slide]

14 I referred to this earlier, but we have long
15 estimated, and all of our data is consistent with this, that
16 the total potential duration of this third stage is seven
17 years but usually we are catching these individuals past
18 midway through the stage and they are converting in the
19 subsequent two- to three-year interval to stages of
20 Alzheimer's disease.

21 [Slide]

22 As I have noted, we have been studying these stage
23 3 individuals in many, many different ways for many years.
24 I want to share these studies very quickly with you. This
25 is work that we published in the 1980s, and we asked the

1 person, "what kinds of problems do you have with memory?" to
2 rate those problems. I referred to this earlier, but the
3 magnitude of rating is actually highest in the GDS 3 stage.
4 It peaks as compared to the subjective complaints and also
5 as compared to subsequent stages of Alzheimer's disease when
6 patients deny. So, complaints of memory impairment are very
7 real in this MCI stage.

8 [Slide]

9 This is other work published in the '80s, and this
10 is important. Using a host of different measures, persons
11 in the third stage, in the MCI stage, do worse on a host of
12 different measures. The first example shown here is the
13 Mini-Mental State. Individuals in stage 3 have significant
14 declines in MMSE scores. Typically, their MMSE scores in
15 the various studies I will be showing are from approximately
16 a mean of 25 to a mean up to 27.5. But, there is a
17 significant decline in Mini-Mental State scores. This is in
18 contrast in all cases to stages 1 and 2 where these tests do
19 not differentiate.

20 [Slide]

21 A host of different tests -- this is from that
22 1998 publication -- also significantly distinguish stage 2
23 individuals, subjective complaints only, from stage 3
24 individuals, MCI individuals. So, many, many different
25 tests, a majority of tests show significant discrimination

1 in this diagnosis.

2 [Slide]

3 Of course, a comprehensive psychometric battery
4 will also significantly discriminate the stage 3 subjects
5 from the subjective complaint only subjects.

6 [Slide]

7 Very importantly in terms of the discussions
8 today, not only did these subjects who changes on test
9 measures and cognitive measures, they also showed changes on
10 many other kinds of measures. So, the work shown here is
11 work which was published in The Journal of the American
12 Geriatrics Society, in 1999 by Franssen and associates.
13 What this shows is that balance and equilibrium measures,
14 measures of tandem walking, putting one foot in front of the
15 other, measures of foot tapping, measures of pronation,
16 supination, turning the hands back and forth, or finger-
17 thumb apposition -- all of these measures significantly
18 distinguish the stage 3 individuals from stage 1 and 2
19 individuals, the MCI individuals from normal aged
20 individuals.

21 [Slide]

22 Interestingly, even neurologic reflexes will
23 distinguish these individuals.

24 [Slide]

25 So, the work shown here is deep tendon reflexes,

1 what we just saw. Even simple deep tendon reflexes, the
2 reflexes that we get with a reflex hammer, will show a
3 significant increase. This is from The Archives of
4 Neurology, in 1991, a study of Franssen and associates, will
5 show a significant increment in the stage 3 subjects as
6 compared to the stage 1 and 2 subjects. So, even neurologic
7 reflexes significantly discriminate this MCI stage.

8 [Slide]

9 Other kinds of reflexes also show changes. So,
10 one gets a significant increase in what are called
11 nociceptive reflexes. This is the snout reflex and the
12 palmomental reflex -- again, a significant increase in this
13 mild cognitive impairment stage and, interestingly, not
14 increasing linearly subsequently. This is when it happens.

15 [Slide]

16 Very interestingly and importantly because of the
17 limitations of cognitive test measures in diverse patient
18 populations, motor measures also show significant changes in
19 this MCI stage. So, this is work published by Kluger et
20 al., in The Journal of Gerontology, in 1997. Here we see
21 the stage 1 and 2 subjects. Here we see the stage 3
22 subjects, performance of the MCI subjects in terms of motor
23 measures such as head tracking, Purdue pegboard and related
24 measures. There is significant decrement in performance,
25 with a further significant decrement in the early

1 Alzheimer's stage 4. If you compare this to a psychometric
2 battery, interestingly, the motor measures do just as well
3 as the psychometric battery in making this discrimination.
4 So, MCI is not only cognition; it is not only memory; it is
5 also motor measures.

6 [Slide]

7 Indeed, eletrophysiologic measures distinguish.
8 So, here we see quantitative, computer analyzed EEGs. One
9 can literally see that the stage 3 individuals, in terms of
10 increase, slowing increase, actually are a different species
11 literally from the stage 2 and the stage 1 individuals. So,
12 there is a change in that parameter.

13 [Slide]

14 This is work published last year from Golomb and
15 associates. This is a special group of MCI subjects with
16 concomitant normal pressure hydrocephalus, and this is a
17 snippet of brain looking for Alzheimer's pathology in a
18 snippet of brain. One sees Alzheimer's pathology in about
19 20 percent of the MCI subjects, with increments in
20 subsequent stages of Alzheimer's disease.

21 [Slide]

22 Very importantly, these symptoms are accompanies
23 by emotional changes. So, anxiety regarding upcoming events
24 -- if a patient has an appointment to see their doctor, the
25 patient in this stage, in the MCI stage, will ask again and

1 again, "when are we going? When are we going? When are we
2 going?" And, this sometimes is a big problem for the
3 spouse. It literally and metaphorically drives the spouse
4 wild. This kind of symptom occurs at about the same level
5 as in any other stage of the disease at that MCI stage.

6 [Slide]

7 Other anxieties actually peak in the MCI stage.
8 These are anxieties regarding such things as memory and also
9 anxieties regarding such things as money.

10 [Slide]

11 Other kinds of behavioral symptoms such as anger
12 also occur in this stage.

13 [Slide]

14 These are results from an ADL scale, the ADL
15 International Scale, which was designed for MCI subjects.
16 What one sees is that in the MCI subjects, the stage 3
17 subjects, as compared to the stage 1 and 2 subjects, there
18 are significant decrements in performance of activities of
19 daily living in the 13 different areas measured in this
20 scale. So, there are significant decrements in
21 concentration, recreation, self-care, household activities,
22 etc. when the questions are very sensitively worded.
23 Sometimes is 1. So, this is at a level of half of sometimes
24 in sensitively worded questions.

25 [Slide]

1 For the 40-item scale there is a significant
2 change in the MCI subjects in ADLs as compared to the normal
3 aged subjects in this international, European and American
4 study.

5 [Slide]

6 Here we see concordant ordinal measures in the
7 stage 3 subjects. What one sees when one applies such
8 measures, and we have just seen this with a host of other
9 data, is that there is nothing magical about memory
10 problems. One sees concomitant concordant ordinal changes
11 in functioning, in praxic ability, shown here, as well as in
12 memory and, obviously, orientation and concentration and
13 other areas. So, in dementia there are generalized changes
14 in cognition. This is the definition of dementia. It
15 applies to MCI. One can define this in terms of memory, but
16 it needs to be understood that that is an arbitrary
17 definition; it is not inherent to the disorder.

18 [Slide]

19 In terms of our questions, can MCI be clearly
20 defined in a clinical setting? Clearly, I think the answer
21 is yes.

22 [Slide]

23 Are there valid criteria for a diagnosis of MCI?
24 I think clearly the answer is yes.

25 [Slide]

1 Can MCI be distinguished from Alzheimer's and
2 other causes of dementia? When defined as MCI of the
3 Alzheimer's type, using the Alzheimer's exclusion criteria,
4 MCI seems to be on a continuum with Alzheimer's disease.

5 [Slide]

6 What outcome measures are appropriate to use in
7 clinical drug trials conducted in MCI? Well, in addition
8 certainly to cognitive measures and to psychometric
9 measures, certainly I think functional measures are
10 important and they need to be functional measures which are
11 sensitive, clearly, to this area. I think behavioral
12 measures are also important and, obviously, they will need
13 to be behavioral measures which are sensitive to this area.

14 In generalizing to other patient populations,
15 there is a danger in applying psychometrics to populations
16 which are different from our research center populations.
17 One might have to utilize some of the other modalities that
18 I have presented examples of in endeavoring to apply MCI to
19 these wider populations, non-cognitive modalities.

20 [Slide]

21 Should clinical drug trials in MCI incorporate any
22 features in their design? The answer is yes, they should
23 incorporate features which are special and especially
24 sensitive to MCI, and special in that way, but otherwise
25 traditional domains, when fully incorporated, including

1 functioning and behavior, apply. Thank you.

2 DR. KAWAS: Thank you. The floor is now open for
3 questions. Dr. Petersen?

4 DR. PETERSEN: Barry, what is your definition of
5 MCI?

6 DR. REISBERG: The definition used here is a
7 global definition. It is a GDS stage of 3, which means that
8 the individual is presenting with subtle deficits, and then
9 those are defined either in cognition or functioning.

10 DR. PETERSEN: So, it is really different than
11 what we have been talking about for the majority of this
12 morning with regard to, for example, amnesic MCI. Amnesic
13 MCI may be embedded in yours but you are really talking
14 about GDS 3 as the defining characteristic, and you are
15 labeling it MCI. I think it varies a fair amount. I mean,
16 this isn't even the same as what Steve was talking about
17 earlier. He was talking about just one form of MCI when he
18 was discussing your data.

19 DR. REISBERG: This data proceeds from the
20 definition of MCI as a GDS stage 3 and looking at the entity
21 from that perspective. So, it is a different way of looking
22 at the entity. Obviously, looking at the entity beginning
23 with memory impairment, one will get certain kinds of
24 results.

25 DR. PETERSEN: Right.

1 DR. REISBERG: But, if one looks at the entity as
2 a global entity, looking for earliest clinically manifesting
3 impairments, then these are the kinds of results that one
4 gets.

5 DR. PETERSEN: Right. So, it really needs to be
6 interpreted in that light, that this is a different set of
7 criteria than what we have been talking about for the most
8 part. We use the GDS and the CDR as severity rating scales
9 after we have made our clinical diagnosis. So, normal MCI,
10 AD, whatever the host of clinical diagnoses, and then we use
11 the scales to grade severity, and when we do it in that
12 fashion our MCI people come out as 2 or 3, maybe 2.5.
13 Similarly on CDR, they come out mostly 0.5. The point being
14 that the rating scales may or may not map onto the clinical
15 criteria. So, there are different ways of using the scales.

16 DR. REISBERG: Of course, it is good to clarify
17 these points but, you know, I would also have a question.
18 How could a person with subjective impairments only meet the
19 criteria for MCI? Could they meet the criteria?

20 DR. PETERSEN: If it is only subjective, but if
21 that is all they present with and then they have a
22 neuropsychological substantiation of that then they are
23 imparied.

24 DR. REISBERG: I see.

25 DR. PETERSEN: But all they have is the subjective

1 impression. The other thing is that in your one-year slide
2 you showed that your GDS 2s still progressed at a rate of
3 14.2 percent over three to four years. That is pretty high.

4 DR. REISBERG: Yes, I do believe there is action
5 there. I do believe that subjective complaints have
6 meaning. In fact, that is why we have differentiated from
7 individuals without subjective complaints. You know, I
8 think ultimately differentiating which of those individuals
9 will go on will be of interest to audiences such as this
10 some years from now.

11 DR. PETERSEN: As an aside, and I don't mean to
12 get off track, when we looked at our normals -- not our MCIs
13 but our normals, and followed them longitudinally, some of
14 them became demented over the years, and it turns out that
15 our normals who did not have an objective memory impairment
16 but did have a subjective memory impairment via the GDS 2s
17 that, in fact, predicted who was going to become demented
18 down the road from normals to dementia.

19 DR. KAWAS: Then, can I ask both of you, first Dr.
20 Reisberg and the Dr. Petersen, how did you elicit the
21 subjective complaint and decide if the answer was yes,
22 subjective complaint or no?

23 DR. REISBERG: We do it, first of all, just the
24 way the CDR has a semi-structured assessment, we also have
25 the semi-structured assessment in performing our global

1 ratings. So, we ask, "do you feel like your memory has
2 declined in comparison with your performance five or ten
3 years ago?" And, that is one question. But we also ask,
4 "do you think that your concentration has declined in
5 comparison to five or ten years ago? Do you think that your
6 orientation has declined? Do you think that your past
7 memory has declined? Do you think that your functioning has
8 declined?" So, we ask those different questions in
9 eliciting subjective complaints of impairment and then we
10 come to a clinical conclusion as to whether there are
11 subjective complaints or not.

12 DR. KAWAS: So, after you me ask all those
13 questions and I say yes, does that mean I am a GDS of 2?

14 DR. REISBERG: Well, the clinician makes the
15 ultimate judgment. In other words, if I asked you those
16 questions and you said yes --

17 DR. KAWAS: I will.

18 [Laughter]

19 DR. REISBERG: -- then I would, as a clinician,
20 try to interpret the circumstances.

21 DR. KAWAS: Fourteen percent in three years? I
22 think Dr. DeKosky has a question and then Dr. Duara.

23 DR. DEKOSKY: We are ultimately faced with the
24 question of where you draw a qualitative line that this
25 person has MCI, or this person has normal age-associated

1 memory impairment, or this person has, as Ron's diagrams
2 suggest, MCI versus Alzheimer's disease. It is a grey
3 shading, and we are asked to draw a line somewhere, and much
4 of what you asked about is not so much where is the line but
5 are you sure that the grading means that they are moving
6 along this course.

7 One of the things that bothers us, and since Barry
8 has listed out a number of the subtleties that he sees in
9 these cases, we will look at people and see a single domain
10 memory impairment MCI, but there are patients many times who
11 don't have a subjective memory complaint, they vigorously --
12 vigorously -- deny that they have any problem and they act
13 as if they don't have any problem and are appropriately
14 annoyed that someone is intruding, and so forth. We have
15 discussions about whether that represents an executive loss
16 and, by definition, is a second domain because we certainly
17 have people who have memory loss who do recognize the
18 severity of it that are about the same and we would say,
19 okay, these people don't have any trouble recognizing the
20 fact that they have a severe memory problem. Those two
21 kinds of people are different, and Devanand published a
22 study a couple of months ago in AGP about those, and I would
23 be curious about yours and Ron's comment about the extent to
24 which the remarkable lack of recognition and denial
25 represents a second domain with respect to potential frontal

1 lobe pathology.

2 DR. REISBERG: First of all, denial exists at all
3 points certainly of the illness. One sees denial very
4 clearly beginning with early Alzheimer's disease. It is
5 hard for us to see denial in our studies prior to early
6 Alzheimer's disease. In all of our studies we see
7 complaints prior to that point, subjective complaints of
8 impairment, and this is true in both the stage of subjective
9 complaints and also in the stage of MCI. But, certainly,
10 one can begin to see denial after that point in terms of the
11 person's moderating their view of the nature of problems.

12 We have actually studied this in great detail by
13 asking spouses about the person's memory problem and asking
14 patients about the person's memory problem. Even in
15 spouses, of course, one also sees denial. So, it is
16 interesting. When you ask spouses how big a problem does
17 the person have with memory, the spouse's complaints
18 actually peak in the early Alzheimer's stage. But then the
19 spouse's complaints level off as they acclimate and the
20 disease doesn't get worse. Then, when the behavioral
21 problems come in subsequently, then the spouses again say
22 the problem is getting worse. So, you see a little bit of
23 acclimation and denial in spouses as well as patients. Does
24 this answer your question?

25 DR. DEKOSKY: No. It may be because I am not a

1 psychiatrist and so I have, I guess, a less operational
2 definition of denial. The family denial about it has a
3 variety of origins. I recognize that. But the impressive
4 thing to me is the difference between a real estate
5 executive who comes in, worried sick because he has a poor
6 performance on recent memory; has noticed it growing and now
7 is clearly dysfunctional; doesn't have other problems that
8 we can identify but is very concerned and has always been
9 aware of it, versus an accountant who comes in who clearly
10 has an identifiable deficit on formal testing; has never
11 complained; always has felt that her memory is okay; is
12 annoyed that her family has brought her in. And, these
13 cases of denial is the part that we have this discussion
14 about because we see both ends of this spectrum in the
15 patients, not the family. I agree that is a different issue
16 with the caregiver. We were constantly wondering if this is
17 a second domain in these people, that they are presenting in
18 fact with two domains, one of which is a frontal lobe or
19 executive function related problem, versus someone who
20 purely has the memory loss but still has intact insight and
21 is able to recognize they have the disorder.

22 DR. REISBERG: In answer to your question, as you
23 know, we do a lot of imaging work. We have never been able
24 to localize any of that in our work.

25 DR. DEKOSKY: If you were able to localize

1 insight, we would be happy to look at that paper --

2 [Laughter]

3 DR. KAWAS: Dr. Katz?

4 DR. KATZ: Just a question, could denial be a
5 personality trait? There are plenty of people who deny all
6 the time. Is there something specific about the nature of
7 this denial that would suggest that it is biologically based
8 or a second function that is cognitively impaired?

9 DR. REISBERG: Denial is universal. We all deny.
10 You know, if you lose an arm or a leg or a loved one, you
11 know but you don't want to know. It is an active process.
12 It is not that you don't know. It is not repression, if you
13 will; it is an active process. You know that it is gone but
14 you don't want to know so you push it out of telling people
15 about it. The loss of a mind is a terrible, terrible,
16 terrible thing, and it is too terrible for most people for
17 conscious contemplation. So, they know but they don't want
18 to know. They don't want you to know. And, a lot of the
19 systems in the disease are based upon this, a lot of the so-
20 called delusions in the disease are based upon the person's
21 denial and desire not to be as impaired as they are. So,
22 patients will say that their parents are alive and that
23 provides them with comfort. Patients will say that they are
24 still working when they are not and that provides them with
25 dignity. So, denial comes out in many, many different ways

1 but it is very much a part of all of us.

2 DR. DUARA: In response to Dr. DeKosky's point
3 about denial of memory loss, and also in reference to this
4 stage of GDS 2 where they have subjective complaints only
5 and you don't really find any objective evidence of
6 cognitive deficit, it was my hypothesis to think that the
7 difference between these two groups -- let's just say it is
8 GDS 2 and 3 -- is basically the severity of memory loss,
9 that people who remember what they have forgotten have a
10 milder degree of memory loss and those people who forget
11 what they have forgotten are the ones who deny. They just
12 don't remember it and they say I didn't forget. They have
13 just forgotten what they have just forgotten.

14 So, I tried to evaluate that with our subjects,
15 and I think the problem that I have come up with is that at
16 that level the memory testing that we do neuro-
17 psychologically is not sensitive enough to pick up the
18 different degrees of memory impairment that occurs. But I
19 was very interested to see the study that was done in the
20 Amsterdam study of the elderly, published by Geerlings in
21 1999, but I just saw it recently. They looked at people who
22 had subjective complaints of memory impairment and on
23 testing were cognitively completely normal, and followed
24 them up over a period of time. They looked at a parallel
25 group of people who had cognitive impairment and either

1 complained or didn't complain of memory impairment. And, it
2 was only the people who did not have cognitive impairment on
3 testing but who did have subjective complaints that
4 progressed towards dementia three years down the line. So,
5 there was a biological reason, if you will, for those people
6 to be complaining. They seemed to be aware of the cognitive
7 deficit that was occurring. They were not denying it, if
8 you will.

9 DR. REISBERG: Let me just say the study of
10 Geerlings, published in The American Journal of Psychiatry,
11 I believe in '99, was exactly as you say, supportive of the
12 idea that subjective complaints of cognitive impairment may
13 have prognostic meaning. It sounds like longitudinal data
14 that we have been engaged in, and also it sounds like, Ron,
15 you have similar data which indicates that these subjective
16 complaints may have meaning. But it is also important to
17 emphasize that this is very, very different from the
18 prognosis of MCI however one defines it. There, the
19 prognosis is much more dramatically malignant.

20 Another aspect of the subjective complaints is
21 that we now have 20-year follow-up on our subjects, and we
22 have an adage which indicates the general benignness of these
23 symptoms, "once a 2, always a 2." Many of these persons do
24 not decline. On the other hand, when we look at our five-
25 year data and when we have a definition of MCI, we begin to

1 see decline to MCI or dementia in about a third of these
2 individuals. So, once one understands MCI, then we can
3 begin to understand what is before MCI.

4 DR. KAWAS: Thank you. Our next public speaker is
5 Dr. Tony Waegeman, UCB Pharma, who is speaking on MCI is a
6 clinical entity: overview of design issues.

7 MCI is a Clinical Entity: Overview of Design Issues

8 DR. WAEGEMAN: Thank you.

9 [Slide]

10 I want to express my gratitude to be able to
11 expose here the work that we are doing with a study
12 implementing concepts of MCI in an ongoing study in Europe.

13 [Slide]

14 When we started this study, of course, a lot of
15 the data that were discussed today were not available, and
16 we worked very intensively with an advisory board of
17 international experts.

18 The way we are implementing MCI in our study is
19 that we start from MCI as a very early stage of dementia,
20 with as the main characteristics that it is a progressive
21 impairment of cognitive function, so a decline from a formal
22 pre-morbid level, leading in a vast majority of patients to
23 more severe and overt forms of dementia, be this Alzheimer's
24 dementia or vascular dementia, mixed forms or other forms of
25 dementia. It has to be stressed, and Dr. Reisberg already

1 mentioned this, that mild is absolutely not equivalent to
2 benign but that MCI is malignant in its prognosis.

3 [Slide]

4 MCI is for us not a psychometric construct but a
5 clinical entity that can be diagnosed using established
6 clinical techniques, for instance dementia staging
7 instruments, and we are using CDR 0.5 in our study but I
8 think that GDS 3 is nearly equivalent. The advantage of
9 such clinical diagnostic measures is that it includes a
10 clinical interview of the patient, bedside mental tests and
11 also, very important, collateral source information.

12 [Slide]

13 Psychometrics can be used in addition to confirm
14 the diagnosis, and from the early data from the first 100
15 patients that we have included in the study we can say that
16 the clinical diagnosis based on the CDR is very much
17 confirmed by psychometric testing, and only a few
18 individuals are rejected due to this additional psychometric
19 criterium. It can also be used to increase the proportion
20 of patients declining and we are using mostly delayed recall
21 or executive function control processes for this purpose.

22 [Slide]

23 So, what is the place of psychometric testing in
24 MCI? I think that psychometric testing is a breakthrough in
25 defining the concept but it is not an ideal tool for a

1 diagnosis. One of the problems is that psychometrics does
2 not give a reliable reference to pre-morbid levels of
3 functioning; that there is an inclusion of patients that
4 always underachieve; and that we don't get those individuals
5 that are declining from a higher level to a level that is
6 still above the window set by psychometric testing. So, we
7 prefer a clinical diagnosis and this is in line with how the
8 disease is diagnosed so it has high face validity. It can
9 better assess the decline from pre-morbid level functioning
10 and it can also identify all sorts of external influences,
11 like physical illnesses, that lead a number of patients to
12 stable MCI or even reverting to a normal function.

13 [Slide]

14 Cognitive testing is very important in MCI and in
15 our study we implement a clinical diagnosis and, on the
16 other hand, we are using cognitive testing as the ideal
17 endpoint for longitudinal follow-up. It is ideal because it
18 gives the possibility to have a detailed measure and a
19 measure that can be repeated over time, something that
20 cannot be done with, for instance, the criterium of
21 conversion. Cognitive testing has been shown over the years
22 to be sensitive to change and to correlate very closely with
23 the increasing levels of clinical severity of dementia. It
24 also correlates very closely with measures of cerebral
25 atrophy or other measures of the Braak staging, for

1 instance, and it is also very good correlation with
2 volumetric MRI measures, and it can be done using
3 standardized and well-validated methods.

4 [Slide]

5 So, I think that cognitive decline over time is
6 the core problem of such patients. We are always speaking
7 about cognitive decline. Although in the very early stages
8 of dementia memory problems seem to be predominant, other
9 cognitive functions are also deteriorating in these early
10 stages in a various proportion of patients at varying speeds
11 in the individual patients. So, evaluations of this
12 cognitive function must cover a full range of cognitive
13 aspects and, of course, tests should be chosen to measure
14 the functions that at these early stages are in decline.
15 For instance, ADAS used in established dementia has a
16 ceiling effect. Although there are already small problems,
17 it is not sufficiently sensitive in this very mild cognitive
18 decline.

19 [Slide]

20 The principal endpoint that we are using in our
21 study is a complete cognitive battery measuring different
22 key aspects of cognition, and I think the tests were
23 mentioned all through the day, tests of free and cued
24 recall; delayed memory; working memory; very important,
25 executive function, planning and problem solving; semantic

1 category fluency; praxis and spatial ability; attention and
2 concentration. So, these measures are more cognitive global
3 function and, of course, all these cognitive batteries
4 should result in one composite score that is covering the
5 whole aspect of global deterioration.

6 [Slide]

7 I think also that parallel to studies in
8 established dementia there should be a global evaluation of
9 change, a CIBIC like measure, and an assessment of
10 instrumental or complex activities of daily living, MCI
11 type. In our study we also use as additional endpoints
12 CIBIC plus GDS as an additional staging instrument. We are
13 using the MMSE to situate the patients at the beginning of
14 the study and at the end. We have an MCI version for
15 activities of daily living and, in line with what Dr.
16 Reisberg was saying, we have a scale for emotional distress,
17 a brief symptom inventory to catch these early behavioral
18 problems that are very clearly present in this population.

19 [Slide]

20 So, that is the design that we are presenting.
21 Placebo and a cognitive battery at screening and at
22 baseline. This run-in period has to control for a learning
23 effect, one of the problems of cognitive testing or
24 psychometric testing. Then we have a one-year treatment of
25 the patient with testing at six months and repeated measures

1 at six months and one year.

2 [Slide]

3 The conclusion of our work -- these are the
4 different elements that we and our advisory board think are
5 appropriate for evaluating drug effects in MCI and should
6 be, in our view, included in potential guidelines. We are
7 opting for a design that is a randomized, parallel group
8 design, a placebo-controlled study of one year duration and
9 a diagnosis based on a clinical diagnosis using dementia
10 staging instruments, and with efficacy endpoints of
11 cognitive decline documented by using a single composite
12 score from a global cognitive test battery, supported by a
13 global clinical measure of change, and/or the impact on
14 instrumental or complex activities of daily living. Thank
15 you.

16 DR. KAWAS: Thank you very much. The floor is now
17 open for questions. I guess it is more of a comment than a
18 question, but I was impressed by your decision to define it
19 clinically the way we define most of the other disorders
20 that we prescribe drugs for rather than operationally with
21 psychometric testing. But it is not clear to me how you
22 train people to do this. In your study, are you actually
23 just using the CDR and the CDR interview, or did you do
24 something differently?

25 DR. WAEGEMAN: We are using basically the CDR

1 with a structured interview and we are, of course, going to
2 investigators meetings where everyone is trained in the use
3 of the CDR. The selection of centers I think makes life a
4 little bit easier, and we are going for centers that are
5 mostly memory clinics so people are used to using this
6 instrument. The centers aren't exactly looking for patients
7 themselves. They are using referrals but the diagnosis is
8 made by people who have certain experience in using these
9 instruments.

10 DR. KAWAS: And, if drugs were to be used for
11 these things, how would you imagine training the clinicians
12 to do the same thing?

13 DR. WAEGEMAN: That is always the difference
14 between the ideal situation of a clinical trial and real
15 life, but I think it was already mentioned today that ten
16 years ago, twenty years ago there was a difficult problem in
17 diagnosing dementia. We think that we have now solved this
18 problem. Maybe in five years time we will be a lot further
19 in teaching how to diagnose MCI.

20 DR. KAWAS: Introduce yourself.

21 DR. IDDON: I am Joanna Iddon, from Cambridge, in
22 England. I just wanted to ask one question, which is
23 something I come across regularly in trying to design trials
24 and choosing which test to use. You mentioned that you
25 should use the composite score to get a global measure. Do

1 you use just that or do you use individual measures too
2 because, surely, by just the composite score you dilute out
3 the specificity?

4 DR. WAEGEMAN: What we decided in our study is to
5 go, as a principal endpoint, for a composite score, but it
6 is evident that we will use the different measures to study
7 the population and to see what happens in this population.
8 But the primary endpoint, the point where we will decide
9 whether or not the drug is making a difference over placebo,
10 is the composite score.

11 DR. IDDON: Will you not wash out the effects by
12 doing that if you have different levels of function in
13 different areas?

14 DR. WAEGEMAN: Since the early problem is a memory
15 problem and more and more cognitive decline is added, I
16 think that using a more global battery will, in fact,
17 accentuate the decline in this population.

18 DR. IDDON: Thanks.

19 DR. KAWAS: Dr. Wolinsky?

20 DR. WOLINSKY: I assume, because of the duration
21 of your trial, that the question you are addressing is
22 really one of symptomatic benefit and not this other issue
23 of progression, or are you planning an enormous number of
24 patients?

25 DR. WAEGEMAN: We are planning 200 patients per

1 group. But to answer your question, I think that the first
2 question that we are asking ourselves is symptomatic and we
3 are not trying to make any distinction between interference
4 with the mechanism of the disease.

5 DR. WOLINSKY: So, then your projections for
6 sample size are based upon an improvement over baseline?

7 DR. WAEGEMAN: Our assumptions are that we have
8 less decline than the placebo group. That is what the
9 sample size is calculated upon.

10 DR. PENIX: Could you briefly elaborate on your
11 MCI version of the instrument on activities of daily living?

12 DR. WAEGEMAN: It is the Glasgow version.

13 DR. GRUNDMAN: The reason that we picked
14 Alzheimer's disease as an endpoint for some of our MCI
15 clinical trials is because of the relatively consistent data
16 about the progress to 15 percent per year, or thereabouts.
17 What sort of information do you have on the rate of change
18 on your composite score over one year? For example, how
19 much do people decline on your composite score or change?

20 DR. WAEGEMAN: We had to use data from earlier
21 studies that have not had the same definition of disease.
22 So, we don't know. We took patients in a more advanced
23 stage and then added some variability.

24 DR. GRUNDMAN: I am just a little bit confused
25 about how you powered the study if you don't sort of know

1 what to expect.

2 DR. WAEGEMAN: We tried to do different forms of
3 modeling and I think people call this an educated guess.

4 [Laughter]

5 DR. VAN BELLE: This composite score is predefined
6 or is it going to be data driven?

7 DR. WAEGEMAN: The tests, of course, are
8 predefined and the way this composite score is arrived at is
9 data driven. So, we normalize over the different measures
10 by using a statistical method of normalization. So, it
11 depends on the outcome. That is correct.

12 DR. GRUNDMAN: You are using psychometric testing
13 in the trial but you are not using it to get into the trial?

14 DR. WAEGEMAN: It is a confirmation of the
15 diagnosis. So, when a patient is diagnosed using CDR, then
16 there is additional testing to exclude patients that have
17 memory function that is too good or too bad. But in the
18 practical situation we see that this applies only to a
19 fairly exceptional number of patients.

20 DR. GRUNDMAN: So, in fact, you are actually using
21 the psychometric test in order to get into the study.

22 DR. WAEGEMAN: As confirmation.

23 DR. KAWAS: Thank you very much. We have one
24 final speaker from the public speakers, Dr. Yogesh Shah, who
25 will be presenting the work of Dr. Ruth O'Hara who is from

1 Stanford and is unable to make it today. Dr. Shah comes
2 from Mercy Mayo in Des Moines, Iowa, and he will be
3 presenting work entitled speed of processing, the missing
4 measure in early detection of MCI.

5 Speed of Processing, the Missing Measure
6 in Early Detection of MCI

7 DR. SHAH: Good afternoon.

8 [Slide]

9 I would like to thank Claudia and I think I would
10 like to thank the falling U.S. market. The reason is that
11 Dr. Ruth O'Hara was going to come and talk today but due to
12 the historic fall in the market her plane ticket was
13 cancelled by the department.

14 [Laughter]

15 So, that gave me the chance to talk here.

16 [Slide]

17 I will try to do my best to match her accent as
18 close as possible. When I left India I did not have any
19 accent but in Iowa I developed some.

20 [Laughter]

21 It is hard to do the Midwestern accent. The talk
22 does not follow her handout. Unlike Dr. Petersen's talk,
23 who was the first one, everything he said was in the
24 handout, for mine very few things are. So, try to bear with
25 me. Ask any questions if you have them and I will do my

1 best.

2 What I would like to do in the next seven to ten
3 minutes is basically talk briefly about the importance of
4 early detection; how we can do it. The speed of processing
5 is a new topic for some. I will talk about Dr. Ruth
6 O'Hara's study, how she has done it, and some conclusions.

7 Whether the market is bull or bear, I think all of
8 us have to face the consequences of chronic disease and the
9 financial aspects of the chronic disease. Currently, in the
10 U.S. we spend about a hundred billion dollars. There was a
11 good question from the gentleman from Chicago about the
12 implications of early detection, and here we go. Currently,
13 we use about a hundred billion dollars a year to treat out
14 patients with dementia. If we can reduce or postpone or
15 delay the diagnosis or the treatment part of dementia by two
16 years, approximately in 10-15 years -- and the numbers are
17 very rough -- we will have probably 10 million less people,
18 and financially, if we can delay the admission to nursing
19 homes, and this is admission to nursing homes of people with
20 dementia, if we can delay that by six months we can save six
21 billion dollars a year only in the U.S.

22 [Slide]

23 So, given the financial aspect, financially it
24 makes a lot of sense to detect dementia early, not only
25 financially but socially, of course, and morally it makes

1 sense to have very early detection and, hopefully, early
2 treatment. If we don't do this, if we don't detect dementia
3 early in about 2050 the predictions are that we will have
4 about 16-18 million people in the U.S. alone with
5 Alzheimer's disease.

6 So the next logical question that Dr. Ganguli
7 asked and the chairman asked also is how do we do that.
8 What is the best way for people in the trenches to diagnose
9 dementia early? This is not a statement, it is a question,
10 are neuropsychological measures significantly sensitive
11 enough and applicable in all primary care physicians -- I am
12 a geriatrician, so for physicians in primary care to apply
13 the neuropsychological testing? Currently, the way our
14 structure is now, we get about 15 minutes to see our
15 patients. So, on an average about 7-10 personal primary
16 care physicians do their Mini-Mental Scale Exam, which is
17 supposed to take about 5-7 minutes. Even the clock draw,
18 which takes less than 2 minutes, is not done by most of the
19 primary care physicians.

20 So, the point is, yes, we need to diagnose early.
21 What do we do? Are there any biological measures? We don't
22 have any markers yet in the blood, urine or serum. Do we
23 have any neurological measures, functional MRI, spectroscopy
24 or PET scans? They are available but not for primary care
25 physicians.

1 So that brings us to the new topic of doing
2 something called reaction time. This is an old concept.
3 There is something called processing speed or reaction time
4 which has been studied by NASA and other fields. We all
5 have a slow decline in the speed of processing. The
6 batteries have to be changed. The same thing happens. At
7 the end of the day the battery goes down.

8 [Slide]

9 If we can have a measure of this reaction time or
10 the speed of processing, which is sensitive enough, easy
11 enough for primary care physicians, and if we can apply it
12 and pick up early cases, that might be very useful.

13 I have a couple of quotations from here. They are
14 not very evidence-based, double-blind, placebo-controlled
15 type but there is enough literature support to say that,
16 yes, there might be some value to look into the speed of
17 processing.

18 [Slide]

19 There are some recent articles from Nature and
20 Neuroscience where research suggests that speed of
21 performance may reflect the efficiency of mental processes,
22 and a similar concept even for patients with MCI.

23 [Slide]

24 So, based on this, even a minute change in speed
25 of processing, about a hundred milliseconds, can make a

1 difference between healthy and non-healthy or MCI or some
2 other form of disease.

3 [Slide]

4 So, this was the basis for Dr. Ruth O'Hara's
5 paper, which was studied at Stanford with support from
6 Cognitive Care. Slow reaction time on memory tests is
7 associated with the presence of apolipoprotein E4 allele.
8 So, I will just summarize the article.

9 [Slide]

10 The objective of the study was to find out the
11 ability of a computerized program on neurocognitive tests,
12 the Cognometer, to differentiate between cognitive
13 performance of subjects with and without apolipoprotein E
14 allele. Along with the speed of processing, especially for
15 those in the back, this is speed of reading also. So, you
16 need to finish this in less than one minute.

17 [Slide]

18 I will summarize for you that the abstract of the
19 paper. It is that the apolipoprotein E group was
20 significantly slower in performing all delayed memory and
21 specific working memory tasks, although there was no
22 significant difference in their accuracy. So, the speed
23 went down but the accuracy remained the same.

24 [Slide]

25 The reaction time performance on memory measures

1 might be able to detect subtle memory deficits, particularly
2 in younger or older adults.

3 [Slide]

4 This is a small number. They used 10 patients
5 with positive apolipoprotein E4, and there were 17 similar
6 adults without the apo 4. They had 3 and 3. The average
7 age was 74. Their average education was about 16 years.
8 The Mini-Mental State Exam was 26.

9 [Slide]

10 So, these are the three structures where they
11 studied the patients with apolipoprotein 4 allele. This
12 column is without the 4 allele, 3 and 3, and this is their
13 pre-value. This is their mean reaction time in
14 milliseconds. These are the factors which were studied by
15 Dr. O'Hara's group.

16 If we can focus on the working memory speed and
17 the working memory capacity, we can see there was
18 significant p-difference. The p value was 0.001.

19 [Slide]

20 If we look at this in a graphic form, this is the
21 milliseconds. These are the factors which were studied.
22 The yellow bar or the orange bar, depending on how far you
23 are from the screen, is the 3 and 3 which is the non-
24 apolipoprotein 4 allele.

25 [Slide]

1 If you compare that to this, the smaller group
2 with 3 and 4 had significant change, meaning that their
3 speed of processing was higher for working memory speed --
4 for most of them but very significant for working memory
5 speed and working memory capacity.

6 [Slide]

7 So, the conclusion by the authors was that, as was
8 seen by the previous presentations by Dr. Petersen and Dr.
9 Duara, the apolipoprotein E allele by itself can be a marker
10 for possible MCI. So, individuals with the apolipoprotein E
11 allele have greater difficulty with the information
12 processing involved with executive memory functions.

13 [Slide]

14 And, the reaction time performance on memory
15 measures might be able to detect subtle memory deficits,
16 especially in the younger older group.

17 [Slide]

18 So, with that, I would like to bring my last
19 slide, and some of the questions have been asked before by
20 the previous speakers. These are similar questions. I
21 didn't have a chance to change them.

22 Is there a frontal executive deficit in MCI? Dr.
23 Ganguli asked that question. If so, are our standard
24 neuropsychologic instruments, whatever we will use either in
25 our institutes or in our private practice, sensitive enough

1 for working memory deficits? And, the last question of the
2 day, can reaction time measure be a meaningful outcome in
3 some of the anti-dementia drug trials?

4 With that, I would like to end. Before you open
5 the floor for questions, Dr. Ruth O'Hara mentioned she would
6 be here by train tomorrow. So, if you have any questions
7 left for her, you can write them down and she can answer
8 them tomorrow.

9 DR. KAWAS: Thank you very much. The floor is
10 open for questions. Actually, I have a point of
11 clarification. In the subjects that she was studying with
12 apo E4 or non-E4 characterized as older, what is the
13 definition of older? And, were the two groups presumably
14 matched for age, and was this age 65 or 85?

15 DR. SHAH: I guess in geriatrics the old old is 85
16 and above. The young old is 65 to 75 --

17 DR. KAWAS: So, what is older, which is what you
18 called them here?

19 DR. SHAH: Young old is 65, 75. So the younger
20 are the group until the age of 72, the people who were 65
21 and 75.

22 DR. KAWAS: Thank you. Dr. Reisberg?

23 DR. REISBERG: You showed significant decrements
24 in working memory speed and other aspects of working memory.
25 You also showed apparently equally significant deficits in

1 what you called learning memory and also in delayed recall.
2 I wonder how you would compare these measures, and also does
3 all the variance overlap in terms of the different measures?

4 DR. SHAH: Sorry, I don't think I will be able to
5 answer these questions in much detail, but if you have
6 specific questions about the treatment itself we can ask Dr.
7 Ruth O'Hara.

8 DR. KAWAS: Do we have any other questions for Dr.
9 Shah? If not, thank you very much for your presentation.

10 Committee Discussion and Deliberation

11 In the interest of trying to get us out of this
12 room before five o'clock, which is my goal, unless there is
13 massive rebellion I think we will skip a coffee break this
14 afternoon and jump right into the discussion. I know some
15 people are going to be trying to catch planes and will be
16 leaving. I think we have had an incredibly excellent series
17 of presentations on the topic, and I am also impressed with
18 the variety of skills and background that the committee
19 brings to these questions. Some of the committee members
20 have worked in this area before and this is, in fact,
21 largely their work that you might be seeing, but we also
22 have the refreshing addition of people who aren't in the
23 area who can look at this from a different perspective and I
24 think that is adding a lot.

25 We have been asked to discuss certain questions

1 that the FDA has asked us to consider in the course of the
2 discussion today. It is my impression that we have actually
3 covered these topics in many ways coming from different
4 directions. But I think now would be a good chance for us
5 to get out on the table any other discussions we have and
6 summarize perhaps the feelings of the committee as well as
7 different individuals in the group who may have different
8 points of view.

9 So, if that is an okay game plan with everybody,
10 the first question that the FDA asked us to consider is can
11 MCI be clearly defined in a clinical setting?

12 At the risk of saying the wrong thing, I believe
13 what happened today was that we heard a lot of different
14 ways in which MCI could be defined. Most of the
15 descriptions were, to date, in the experimental clinical
16 setting, that is, with researchers who make it their
17 business to try and do these kinds of studies with
18 considerable amounts of training. The general consensus, I
19 believe, that came out of the discussion was the feeling
20 that possibly this could be done in the clinical environment
21 with physicians in the same way that we have made the
22 process of diagnosing Alzheimer's disease in the last ten
23 years.

24 But, I would like to open the floor for
25 discussions on can MCI be clearly defined in a clinical

1 setting. Who wants to take the strong approach that it can
2 and summarize their opinion? Dr. Petersen?

3 DR. PETERSEN: I will take a crack at it. I think
4 we found that this can be a heterogeneous concept as well.
5 So, I think if we restrict ourselves to an amnesic variety
6 or the definition of MCI with a prominent memory impairment
7 with relative preservation of other cognitive functions,
8 ADLs and the like, I think that there are enough studies
9 that are sort of coalescing to lead us to believe that this
10 can be done, and that if you define it in that fashion there
11 is a rather predictable rate of progression to clinically
12 probable Alzheimer's disease, again, in the 10-15-plus
13 percent per year range. It appears that most of the
14 clinical trials are using some form of that set of criteria.

15 So, again, that is not proof but it seems to be
16 that this can be done, at least on a multi-center clinical
17 trial basis, which lends some credibility to the reliability
18 of the notion among different centers that they are properly
19 trained. So, I think with regard to the amnesic or the
20 prodromal Alzheimer's disease form of MCI, the criteria
21 probably are fairly reasonably well defined.

22 DR. KAWAS: I know you might be leaving soon so I
23 have a question for you before you sneak out. I mean, the
24 criteria over time, whenever we are defining clinical
25 syndrome, tends to grow. So, you know, subjective

1 complaint, and objective documentation, and a decline in
2 this age and that age -- are we sure that all of those
3 criteria do any better than doing something as simple as
4 taking the tail of the distribution of scores on a simple
5 test like Mini-Mental or the Blessed IMC? I mean, in the
6 '80s Katzman and colleagues published a paper called,
7 "Development of Dementia in an 80-Year Old Cohort." The
8 primary finding was that individuals who had 5, 6, 7 or 8
9 errors, which was the maximum allowed on enrollment on the
10 Blessed IMC test, had about a 10-fold increase of developing
11 dementia within 3-5 years.

12 It seems to me that almost no matter how you have
13 criteria, we can identify a high risk group and I am trying
14 to figure out why we have to get so complicated. Why can't
15 we go to something that is simpler and conceivably could be
16 put into the clinical arena? Or, are you convinced that
17 this wouldn't work as well?

18 DR. PETERSEN: No, I think it is a good question,
19 and I am familiar with that paper. In fact, using the
20 Blessed -- I mean, the Blessed does have some memory
21 component with a little recall component that is pretty good
22 at doing that. So, I think that instrument was tapping into
23 probably the most relevant cognitive domain.

24 It is quite possible this can be done in a primary
25 care setting with relatively simple instruments, but I don't

1 know if that is the case yet. I think in a logical
2 progression, the way this is evolving is that it starts in
3 specialty clinics. Then it moves to a little bit more of a
4 general practice setting and ultimately to whether this can
5 be operationalized for the general practitioner. I think we
6 are still at the former stages right now of nailing down the
7 diagnostic criteria and seeing what happens. But, it is
8 possible. I am a little bit cautious about doing it though
9 because I think it is a reasonably important diagnosis and I
10 am afraid that if you get too broad a brush stroke with your
11 instrument that you may misclassify too many people to make
12 it useful.

13 DR. GRUNDMAN: I think the data that we have seen
14 and that I showed earlier shows that to really get the kind
15 of conversion rates that we are interested in people have to
16 have some sort of symptoms, plus have the objective
17 deficits. If you just look at people who are classified as
18 clinically normal that fall below one standard deviation
19 below normal, you will find that the risk rates for those
20 people are a little bit higher than normals but they don't
21 approach those for people who already fit into the MCI
22 category.

23 DR. KAWAS: By symptoms you mean complaints of the
24 subject or observable memory loss --

25 DR. GRUNDMAN: What I mean is that these are

1 people are at the beginnings of CDR 0.5. You have a box
2 where 0.5 or 1.0, that is, they have memory complaints which
3 are corroborated by an informant and in the clinician's
4 opinion are demonstrating early signs of memory loss. So,
5 that plus the cognitive impairment can dramatically increase
6 the risk of developing AD over people who just have memory
7 impairment alone who are considered normal.

8 DR. VAN BELLE: I guess I am still agnostic on
9 this. I think we have defined a mystery. We have sort of
10 put a fence around the mystery but we have really heard many
11 ways of defining MCI today and I am not sure that there is a
12 consistent operational entity that we can deal with at a
13 relatively simple level. Any time that you begin to qualify
14 diagnoses on the basis of age, plus education, plus other
15 things I think you are really into a very soft area. I am
16 not sure that it is very useful from a clinical point of
17 view to try to do something at this at a national level.

18 From a research level, an institution or a group
19 could come to some agreement as to how they are going to
20 define operationally such an entity and then do some
21 research on that. But in terms of really having a clinical
22 entity, I just haven't seen the evidence yet.

23 DR. REISBERG: Just a word about qualifying
24 diagnoses, you know, for a diagnosis of dementia we have
25 always had to qualify that with a clinical criterion. There

1 has to be decline in performance, clinical decline. We were
2 unable to define dementia for general community populations
3 based on any kind of cut-offs. For example, a Mini-Mental
4 State of 23 -- one can get those kinds of scores in persons
5 who, for example, have less than eight years of education or
6 other similar kinds of, if you will, handicaps or problems.
7 So, for clinical entities in this area we have always had to
8 resort to clinical definitions as well as any kind of mental
9 status or psychometric definitions.

10 DR. DUARA: I think we have heard a number of
11 different definitions, and maybe what we really need is a
12 conference, similar to the one that was developed about the
13 NINCDS ADRDA conference, that came to some kind of a
14 definition and established the diagnosis of Alzheimer's
15 disease, or probable and possible Alzheimer's disease. We
16 can probably do the same thing for MCI. I don't see that as
17 being a difficult job because I think most people here
18 actually seem to be in agreement that there is such an
19 entity. It is just a question of fine-tuning the different
20 definitions and coming to some sort of an agreement.

21 So, I think the clinical definition can be done,
22 although it requires the effort and the involvement of a
23 large number of people to work together. But I think that
24 we can go a stage further too, and I think we can come to a
25 way of evaluating both dementia and MCI in the community

1 using tests, using screening scores and validating them. I
2 mean, I have some data that suggests that you can do that.
3 I think we need a lot more data. It is preliminary data,
4 but I am encouraged by what I have seen so far. And, I
5 think that when you do this kind of thing in the community
6 you are obliged not only to look at cognitive impairment but
7 also to look at depression because the two of them,
8 particularly in elderly people, are often intermingled and
9 one has to figure out which one is responsible for what.
10 But I think this can be done.

11 DR. KAWAS: I don't think anyone would disagree
12 that a consensus conference could be called and we could
13 agree on something and write it down. I guess the part I
14 don't understand is when they did the consensus conference
15 for Alzheimer's disease, I mean, they were doing it for a
16 disease. Would we be defining a disease? Is that what MCI
17 is? Would we be defining a syndrome? Is that what MCI is,
18 like dementia? Or, would we be defining a symptom complex?
19 I mean, we usually do consensus conferences for clinical
20 diagnosis for diseases, and it is not clear to me that we
21 have a disease here. Maybe, in fact, that is the underlying
22 question of all the other things that the FDA would like us
23 to comment on. So, since you have your mike still on, in
24 your opinion, is MCI any of those things? None of them or
25 all of those things? What is it?

1 DR. DUARA: I think it is primarily a symptom
2 complex and that one should define it as such.

3 DR. KAWAS: Like pain, and it could be attached to
4 any disease?

5 DR. DUARA: Well, the DSM has a number of
6 different diagnoses that don't really depend on some kind of
7 pathological diagnosis. They are clinical diagnoses --

8 DR. KAWAS: It is called psychiatry.

9 [Laughter]

10 Excuse me. Go on, I am sorry.

11 DR. DUARA: No, I think I said all I wanted to.

12 DR. KAWAS: Yes, Dr. Weiner?

13 DR. WEINER: Based on everything I have heard
14 today, I think it can be defined.

15 DR. KAWAS: What? Say that again.

16 DR. WEINER: MCI, clinically for the purposes of
17 treatment, for the purposes of studies, although it is
18 heterogeneous for the most part, from what I have heard, MCI
19 really is an early stage of Alzheimer's disease because 80
20 percent of the people end up getting Alzheimer's disease.
21 If you look at multiple sclerosis, you have different stages
22 of MS. You have relapsing-remitting MS; you have
23 progressive MS. Not all people who have relapsing-remitting
24 MS go to progressive MS. There are different drugs approved
25 for relapsing-remitting MS and for progressive MS. There

1 are studies being considered for treating relapsing-
2 remitting MS and preventing people from going into the
3 progressive stage. One could analogously say that there are
4 people with MCI and there are studies to prevent them from
5 getting Alzheimer's, but that doesn't mean that you couldn't
6 have studies to treat MCI itself.

7 I think the only reason that people are calling it
8 a symptom complex, if you will, is because it isn't one
9 hundred percent. There are some people, based on what I
10 have heard, who don't go on and have Alzheimer's disease so
11 that in the 1000 patients that you might diagnose with MCI
12 there might be a couple of hundred that have some other type
13 of issue.

14 I think in terms of drug trials, then you can have
15 different drugs that you are testing for different reasons.
16 There might be some drugs that you might test in an MCI
17 population that is more symptom oriented to help them in
18 terms of their memory, or whatever, whereas there might be
19 other drugs that you are testing in an MCI population that
20 are designed more on the underlying pathology, and there you
21 might be testing progression to Alzheimer's.

22 So, based on everything I have heard, I guess I
23 wouldn't necessarily agree with what you said, that it is
24 just too mixed up. I think there is an entity here and I
25 think it could ultimately be tested for. Obviously, people

1 have to decide what the standards are. I think it could
2 ultimately be tested for in the community and it could be
3 tested for in studies and, in doing so, I think it would
4 help early treatment trials for preventing progression to
5 Alzheimer's and I think it would help in testing medicines
6 that might provide symptomatic relief for these people.

7 I think we also have to be cognizant of the
8 individuals who suffer from this problem -- the families,
9 the social stigma, and I think the issue that the label of
10 Alzheimer's disease or Alzheimer's is not a pleasant one and
11 that segregating them a bit I think can be helpful to the
12 families and to the patients and maybe to the physicians as
13 well in treating these people. I know in multiple sclerosis
14 early on, before we had treatments, we didn't want to say
15 you had MS because you didn't want to say, "oh, my goodness,
16 you are going to end up in a wheelchair." Now we know that
17 many people don't end up in wheelchairs and there are
18 treatments. So, I think it is also very helpful to the
19 people who suffer from this and their families to have
20 something that is a different classification before you get
21 to Alzheimer's.

22 DR. PENIX: I agree with many of those comments
23 that Dr. Weiner just gave. I think that a conversion rate
24 of 80 percent over about a six to seven-year period
25 certainly indicates that the bulk of these patients probably

1 do have early Alzheimer's disease and very likely, from the
2 time courses that we saw, the eventual number that convert
3 to Alzheimer's may be greater than that. I think we should
4 be reminded that many of the Alzheimer's disease studies,
5 which is a clinical diagnosis as well -- in the studies
6 where patients go on to autopsy there is about a 90 to 95
7 percent positive identification of patients with Alzheimer's
8 disease before autopsy. So, again, that is not 100 percent.
9 Even using NINCDS criteria, we are not identifying 100
10 percent of them, but I think 80 percent really gives a very
11 good estimation for MCI.

12 I guess we are going to talk about the criteria,
13 and in regards to the criteria, I think that many people
14 have used the criteria that Dr. Petersen has outlined and
15 there are five points that nearly everyone is in agreement
16 on, four out of five points, and that is that there is a
17 subjective memory complaint, that there is normal general
18 cognitive function, normal activities of daily living, and
19 that the patients be not demented. It appears that the
20 inconsistency is in identifying the objective memory
21 impairment, and that is the thing that there may be some
22 variability in. So, I think the consensus may just focus on
23 how do we identify objectively the presence and the degree
24 of the memory impairment.

25 DR. PETERSEN: I agree with you and I think that

1 highlights one of the key issues and the responsibility,
2 certainly, of people doing research in this area and
3 probably of the agency as well, which is where do you draw
4 the line between normal aging and pathologic memory
5 impairment? And, I think that is a very difficult issue and
6 I think we just don't know enough about cognition in normal
7 aging. We talk about normative data. We use normative
8 data, but we know they are flawed. We know that they are
9 based on certain characteristics of the population. Do you
10 need to age and education adjust them? Does that cause a
11 problem?

12 So, I think the real issue is how can you
13 characterize this condition without getting too loose on the
14 end of the border between normal aging and pathology because
15 all of us in this room probably do not remember as we did
16 two years ago, or five years ago, or something of that
17 nature. So, does that mean? No, it really doesn't. So,
18 you really have to be careful how you define that memory
19 criterion to make sure it really represents a significant
20 abnormality.

21 DR. KAWAS: Does that mean to really see how it
22 represents potentially prodromal, preclinical, early AD?

23 DR. PETERSEN: I think longitudinal studies of
24 aging, longitudinal studies of mild impairment with
25 pathologic confirmation, hopefully, would lend some credence

1 to that. I have to go. I apologize.

2 DR. KAWAS: Thank you very much for all your
3 insights today, Dr. Petersen. Mary?

4 DR. GANGULI: I was quite fascinated by Dr.
5 Weiner's multiple sclerosis analogy and I wanted to
6 understand that a little bit. You are saying that we can
7 now tell people with MS, well, you have MS but most people
8 don't all go the same way and you may not end up in a
9 wheelchair, and you may have a relatively mild outcome. So,
10 now we can tell you, you have MS. Why couldn't we do that
11 with AD? Why couldn't we say to people with what we are
12 calling MCI, you know, "you might have early AD but it may
13 not get very bad and it might not get much worse," rather
14 than giving it a new name?

15 Again, I am a psychiatrist and I don't know that
16 we can allow stigma to determine how we classify disorders.
17 You know, all the names that have come up for mental
18 retardation and the different terms that have been used, and
19 whenever something became pejorative we came up with a new
20 term for it, but it will also become pejorative. That is
21 just what happens in the public eye. In fact, in
22 schizophrenia we try very hard to use that word and we feel
23 that we perpetuate the stigma by avoiding the term and
24 thinking of it as something unmentionable.

25 So, would it not be reasonable to de-mystify this

1 a bit and say, well, there is a lot we don't know but not
2 everybody who has what you have will go on to have full-
3 blown Alzheimer's disease, rather than say you have
4 something for which we are going to come up with a new name?

5 DR. WEINER: I don't think it makes any
6 difference. It is all semantics really. I mean, it is; it
7 is whether you call it relapsing-remitting MS, it is a form
8 of it. This isn't my field, but if people who work in the
9 field wanted to call it early AD or call it mild AD, and I
10 don't think there is anything wrong with that. So, I don't
11 think that is a particular issue but I don't work in the
12 field. I do feel, however, that human nature is what it is.
13 You probably know more about that, being a psychiatry, or
14 maybe less about it --

15 [Laughter]

16 DR. GANGULI: Less.

17 DR. WEINER: But I know just in terms of multiple
18 sclerosis, everybody has his vision of people in wheelchairs
19 and, no matter what you say -- I try to say instead of
20 multiple sclerosis you have singular sclerosis because you
21 only had one attack and there are different types of
22 multiple sclerosis --

23 [Laughter]

24 -- and that type of thing. So, I think it is
25 going to be very hard for the public. I think you are

1 better off using a different term. That is my own,
2 personal, view.

3 DR. GANGULI: Yes, I think I understood where you
4 were going but when you said it was only semantics, I think
5 we have been reminded a couple of times by our hosts at the
6 FDA that semantics are very important for them in terms of
7 labeling and indications, and so on. And, if we are going
8 to say this is a different entity when we think it is the
9 same entity but an earlier stage, we have to be aware of the
10 implications of that. I think that the real concern about
11 MCI is that not everybody who meets the criteria has
12 prodromal AD. Some of them have something else and some of
13 them go on to develop something else and some of them won't
14 get any worse. Some of them may be what someone referred to
15 as "perpetual underachievers."

16 DR. WEINER: Well, the same thing is true in
17 multiple sclerosis. You have some people who have some
18 lesions on MRI and have some attacks and are very benign for
19 many, many years and it might be a different entity. It is
20 just that we don't understand it completely. So, I think
21 that in terms of the semantics, it is the clinical
22 definition and then what name you apply to it depends on
23 what name you want to apply.

24 DR. KAWAS: Dr. DeKosky and then Dr. Wolinsky.

25 DR. DEKOSKY: I think to some extent the MS

1 impression is from the MS advocacy groups early work, trying
2 to get it recognized. I remember growing up and hearing the
3 phrase, "the greatcrippler of young adults" and I didn't
4 know what it meant but I understand now why it was done --
5 to mobilize. And, I think it will take a long time to sort
6 of bring people into an era where there really are therapies
7 and it makes a difference.

8 I have trouble with the semantic argument and I
9 will tell you why. I have trouble with the analogy to MS
10 because all of the AD patients will continue to go downhill
11 unless we come up with medications that are different,
12 whereas with MS, in fact, they may burn out, slow down,
13 stabilize and so forth, or at least, in my view, they have a
14 better chance of that than AD patients do for suddenly kind
15 of stabilizing and not changing.

16 But all of the press inquiries and most of the
17 inquiries that we will get from the families will be, "well,
18 wait a minute, doc, it's 80 percent of people who are going
19 to get the disorder within six or seven years. Doesn't that
20 mean they just have Alzheimer's disease?" And, it doesn't
21 matter how we dress this up for outside, for regulatory
22 purposes we stay within these particular rules. For what
23 happens when you go outside, and it is fair to bring it in
24 here because we are talking about how do you make this
25 diagnosis in the general population, I believe the answer

1 will be it will be generalized wildly.

2 I disagree a bit with Jerry. I think for the
3 amnestic form of MCI the data are remarkably consistent.
4 Even with some mild differences in exactly how we define or
5 we do our cut-offs, those cases very consistently come in as
6 impaired. For another group of people in whom I think the
7 clinical suspicion is the person has some kind of
8 progression of their cognitive impairment, that is, they
9 come to the doctor with a history that this has been
10 gradually coming on -- I would separate those from the
11 infarction type of cognitive impairment or the more static
12 forms that are part of what comes to every clinic. Those
13 also appear to go down. We have less knowledge of those.
14 But the outcome of those cases also looks like it is going
15 to be very high.

16 The point that I think Jerry asked about earlier,
17 what percentage of the whole population is this of people
18 who are moving toward significant dementia, we don't yet
19 have quite the same concept. We would like to believe that
20 if we looked at everybody we would catch them in their
21 downward flow, but if we look at the normal controls we see
22 that normal controls convert at the rate of 1-2 percent per
23 year. One year they are normal and the next year they meet
24 criteria for AD. So, maybe not everyone passes through more
25 leisurely cognitive impairment.

1 So, I have trouble with that analogy. I do think
2 that no matter what is said with respect to this, and I
3 think the data are telling us that whether we like it or
4 not, this is going to be seen as essentially the entry into
5 Alzheimer's disease. If there is a way to avoid that in the
6 sense of panicking people for the 20 percent who won't get
7 it, I think that would be very useful but these are what the
8 data look like, I think they are remarkably consistent.

9 DR. WOLINSKY: I just want to be sure of one thing
10 in terms of the data that was presented to me before I make
11 the next statement. So, I think I have seen a number of
12 different patient population groups, that is, collected in
13 different centers or consortiums of centers in which,
14 whatever the subtleties of definition have been, patients
15 who all seemed to have this mild cognitive impairment have
16 progressed at an alarming rate over a reasonably short
17 period of time. These are different cohorts. They are not
18 overlapping cohorts. We have looked at about 400-500 or 600
19 patients.

20 DR. GRUNDMAN: Yes, we have collected the data
21 from 17 centers, but I would disagree with the statement
22 that they are progressing at an alarming rate. When you
23 look at these people over a year, over two years, over three
24 years, they are actually progressing at a relatively slow
25 rate. I showed you the data on the Mini-Mental. They are

1 declining by less than a point a year; on the ADAS-COG
2 similarly. They are not progressing the way a typical
3 Alzheimer patient would.

4 DR. WOLINSKY: Sorry, I picked the wrong adjective
5 in terms of "alarming" -- a predictable rate that will get
6 80 percent of the patients into a diagnostic category.
7 This, to me, is the critical issue because then there really
8 isn't a need for very much of a consensus conference to
9 decide how you diagnose minimal clinical impairment. You
10 know, you can just say who spits furthest have the criteria
11 fit. The important thing is that the criteria not be
12 changed in such a way that you lose the power of knowing
13 that 80 percent of this defined population has Alzheimer's
14 disease and will declare themselves within a finite period
15 of time. If that is the case, then, yes, you have defined
16 an early stage -- as you call it, an entry to Alzheimer's
17 disease, and that is important for a certain type of
18 clinical trial design. As I see it, the type of clinical
19 trial design, which we haven't spent very much time on but
20 is the crux of the issue in my concept, is one which is
21 designed at reducing the proportion of patients that enter
22 that next phase of the disease. It is really a true disease
23 modification or preventive paradigm.

24 Now, here is where I think the semantics come in.
25 There probably are plenty of people who would like to also

1 have drugs for minimal forgetfulness, for want of a better
2 term that nobody has used, in which one can design simple
3 symptomatic treatment trials, and the criteria for getting
4 people into that could be whatever they come up to be for a
5 particular trial because the issue is symptom management,
6 not exactly disease pathogenesis management. And, I think
7 these are the issues that probably people in the Alzheimer's
8 field really have to deal with.

9 DR. KAWAS: Can I ask Dr. Grundman a quick
10 question, maybe in keeping with your point, you collated
11 data from 17 sites but, unless I am mistaken, each site had
12 their own way of determining MCI. Since I was one of the
13 sites, I can tell you that the way I did it wasn't like any
14 way that you have heard here today and, despite that, I have
15 almost the same predictive rate as everybody else.

16 I mean, one of the next questions that we are
17 going to be looking at and have sort of scooted into is are
18 there valid criteria for the diagnosis of MCI, and I think
19 what we have heard here today in large measure was it
20 depends on what you mean by validity. Certainly, the
21 predictive validity of almost all the criteria is quite
22 reasonable and quite high. The reliability and other
23 issues, and there is no gold standard validity obviously, is
24 essentially unknown. But I think for the predictive
25 validity it almost doesn't matter how you do it as long as

1 identify the tail of the distribution, which is why I
2 thought that maybe a simple measure, you know, might do
3 almost the same job as some of the more complex things that
4 have been suggested today.

5 We have someone at the mike. If you could
6 identify yourself?

7 DR. COHEN: Yes, I am Perry Cohen. I am with the
8 Parkinson's Foundation, and I think a better analogy than MS
9 might be Parkinson's in which there is progression to
10 dementia. It is probably part of the 20 percent. So, the
11 semantic difference may be a valid one. I also want to
12 comment that NIH is planning on a longitudinal study on
13 neurodegeneration.

14 DR. KAWAS: Thank you very much. Dr. Duara?

15 DR. DUARA: I just wanted to come back from the
16 peanut gallery and talk, now that Ron Petersen is out of the
17 room --

18 [Laughter]

19 -- to say that all MCI is not early Alzheimer's
20 disease. We seemed to be moving in that direction in the
21 last few discussions, but it is not necessarily so. It
22 really depends, and I really want to emphasize this point --
23 it really depends on what population you are studying. If
24 you do these studies in an Alzheimer's disease research
25 center you have already concentrated your population so that

1 they are now likely to be highly Alzheimer-like at different
2 stages, some in the MCI stage and some in the frank dementia
3 stage. But if you go out into the community and you just
4 look at the general population, you look at people who come
5 to a doctor's office with cognitive impairment, you are not
6 going to see that percentage of Alzheimer's disease. You
7 are going to see a variety of different cognitive
8 impairments. So, I think we need to keep that particular
9 notion there.

10 I had mentioned earlier that when we define MCI,
11 yes, maybe 50 percent, depending on the population, 60
12 percent or 70 percent would be early Alzheimer's disease but
13 there is a definite subgroup there that is not early
14 Alzheimer's disease. I am wondering whether Phil Gorelick
15 would like to talk on this as well because I have heard some
16 of his views on this. We are talking about a certain
17 endpoint. It really doesn't matter what the disease is,
18 they all get the same sort of thing.

19 I am sort of being a little bit diffuse in terms
20 of treatment but I think there is good reason to believe
21 that there is a final common pathway by which memory
22 impairment occurs, most cognitive impairment occurs, amongst
23 a number of diseases that affect the brain.

24 DR. KAWAS: Can I ask you a focus question on
25 treatment then? If MCI is a prodrome not just to

1 Alzheimer's disease but whatever -- multiple sclerosis,
2 Parkinson's, dementia, just a bad day -- in terms of drug
3 development would you say then that we should be talking
4 about developing drugs specifically for MCI amnestic, AD or
5 whatever you want to call it, or are you suggesting that we
6 should be looking in terms of treatments for MCI, period, no
7 matter what it is.

8 DR. DUARA: The latter. I am saying that it may
9 well be that the same drugs may work equally well in
10 patients who have different pathological entities but who
11 all present with objective memory impairment.

12 DR. KAWAS: Okay. Dr. Chui is at the microphone.

13 DR. CHUI: Yes, thank you, Dr. Kawas. I wanted to
14 second some of the things that Ron had said because a number
15 of us from this peanut gallery are interested in other types
16 of mild cognitive impairment that might have their origin in
17 cerebrovascular disease. So, I think too that mild
18 cognitive impairment is a heterogeneous syndrome or symptom
19 complex.

20 I wanted to throw another caveat in. I think that
21 because MCI is the frontier now we might be assuming that
22 the diagnosis of Alzheimer's disease is firm. We have
23 dropped the terminology probable Alzheimer's disease,
24 possible Alzheimer's disease, and here we are just using
25 Alzheimer's disease. Some of us have acknowledged that we

1 are saying clinical diagnosis of Alzheimer's disease. The
2 Alzheimer's disease centers have shown that when you look at
3 pathology as the gold standard the clinical diagnosis of
4 Alzheimer's disease is fairly sensitive in research settings
5 but it is not specific. The sensitivity among 28 centers,
6 collectively contributing over 2000 cases of dementia, was
7 about 93 percent sensitive but only 55 percent specific.
8 So, the accuracy was about 85 percent. If you use that in
9 evidence-based dementia terms, the likelihood ratio is about
10 4, which isn't considered a very good diagnostic test.

11 So, what we are really predicting here when we are
12 talking about conversion to Alzheimer's disease is
13 predicting the development from a mild cognitive impairment
14 to a progressive dementia, not Alzheimer's disease
15 necessarily. So, I think, to be honest, we ought to step
16 back a little bit and recognize that we are really dealing
17 with phenomenology and we are talking about dementia of the
18 Alzheimer type -- I am a neurologist but I think the
19 psychiatrists were right. We know it is dementia and we
20 think it is of the Alzheimer type, and we have the NINCDS
21 criteria. Then we are talking about mild cognitive
22 impairment, perhaps of the Alzheimer type or perhaps of some
23 type of vascular dementia or of a Lewy body dementia type.

24 DR. KAWAS: Actually, while you are still at the
25 microphone, Helena, do you think that we can distinguish MCI

1 of the Alzheimer type from MCI vascular, from MCI Lewy or
2 whatever right now?

3 DR. CHUI: I don't think we have the data, but I
4 think it is a legitimate question and we can answer it. I
5 am not opposed to hypothesizing that the memory predominant
6 type is going to go to Alzheimer's disease.

7 DR. REISBERG: Just coming back to Dr. Duara's
8 point for a moment, I think it is very clear from the
9 literature that one can enhance or enrich the population if
10 one seeks to establish a population who is, if you will,
11 enriched for decline. And, one does this by adding
12 additional good measures of MCI, at least for the
13 population. So, for example, we published a study where I
14 showed the Kluger data and that is a very, if you will,
15 elaborate, and I will even use the word rich, study. Their
16 clinical criteria alone -- a GDS stage of 3 as opposed to a
17 1 or 2 -- gives you an 80 percent prediction, a 0.8
18 correlation with change. But that can be enriched by adding
19 a paragraph recall test, the best psychometric measure, up
20 to about 86 percent prediction, overall accuracy in terms of
21 prediction to decline.

22 It does need to be said that that is a special
23 population, that is, a research center population. But one
24 can add other measures. A variety of such measures have
25 been discussed here which can enhance the likelihood of

1 decline.

2 DR. KAWAS: Thanks. Dr. Grundman and then Dr.
3 Wolinsky.

4 DR. GRUNDMAN: From the discussion that we have
5 had today, I think it is clear that there are different
6 types of cognitive impairment that are due to different
7 etiologies, and I think what we have demonstrated is that we
8 can sort most of those etiologies out to define the type of
9 MCI that goes on to Alzheimer's disease.

10 I also think that it doesn't make sense to think
11 about all MCI as a single homogenous entity where we are
12 just going to come up with a single drug or drug type that
13 is going to cure everybody. That might be true in a
14 symptomatic case where you are affecting some non-specific
15 circumstance but if you are talking about the ultimate
16 etiology of the disease and pathophysiologic principles, if
17 you have a drug that works, say, on diminishing amyloid or
18 hyperphosphorylation of tau, it makes no sense to test these
19 in an MCI non-AD type, at least to start the ball rolling.

20 DR. WOLINSKY: I think Michael has just said most
21 of what I wanted to say but, certainly, if it is required
22 that an Alzheimer specialty clinic is necessary in order to
23 define that brand of MCI that leads to Alzheimer's in high
24 probability, and if the question of therapy is to try to
25 retard that, then that is where you study the disease. If

1 it can't be generalized, well, that is all right because
2 eventually, if we get good drugs, it won't matter. But that
3 is part of the process and, unfortunately, none of the
4 studies that I am aware of -- I am sure Russ Katz can
5 correct me very quickly, that come to the FDA where the
6 group that is tested is an adequate sampling of the general
7 population in which the drug will be used, that is something
8 we always have to deal with.

9 DR. KAWAS: Dr. Katz?

10 DR. KATZ: Well, that is true. It depends on what
11 you mean by adequate. It certainly is not necessarily
12 representative, for sure.

13 But, as far as what Michael said, I am not so much
14 concerned about the underlying pathology being the same.
15 Certainly, obviously it may not make sense ultimately to
16 study a particular drug that has a particular mechanism of
17 action or that you think has a particular mechanism of
18 action where you expect that it wouldn't work for the
19 underlying pathology that is not relevant. But from a
20 clinical point of view, if there is a sense that MCI is more
21 than early Alzheimer's disease, a question to me is, is that
22 clinical syndrome that we are calling MCI sufficiently
23 homogeneous clinically, independent of the underlying
24 pathology, so that we can say here is a drug for MCI.

25 Then, the second question is, well, how do you

1 tell people how to diagnose that? I mean, if it is like
2 pain, we know what pain is. That may have different
3 underlying etiologies and pathologies but we can say this is
4 pain. We recognize it and we expect it to respond in a
5 certain way.

6 So, what is important for me to understand is
7 whether or not, if MCI is the result of several different
8 underlying pathologies, some of which we may not even be
9 able to identify, is it clinically homogeneous enough so
10 that we can identify it? If the MCI differs clinically for
11 vascular etiology compared to an Alzheimer's etiology, then
12 we have to ask the question what does drug development look
13 like if you want to get an MCI claim. Do you have to study
14 all the different pathologies and get a specific claim?

15 So, I would like to know whether or not people
16 think that clinically MCI, independent of underlying
17 pathology, is sufficiently homogeneous to be able to
18 diagnose it. Then, if it is, what standards does one use?
19 I think we still need to get back to that a little bit
20 because if it is defined in comparison to a 1.5 standard
21 deviations difference from your age-matched peers, it is
22 hard to write that in labeling. So, I think these are
23 questions that I would like to hear the answers to are least
24 discussion on.

25 DR. KAWAS: Dr. Penix, do you want to comment on

1 that?

2 DR. PENIX: Yes. I think in order to answer your
3 question, Dr. Katz, it forces the issue of separating
4 symptomatic treatment from treatment of the underlying
5 disease process or slowing the progression. To use your
6 analogy with pain, certainly we know that there are
7 analgesics that treat all pains but then, if we have cancer
8 that is causing pain and we want to treat the underlying
9 cancer we use different types of drugs. We use the
10 chemotherapeutic agents. So, certainly, it may be useful
11 for symptomatic treatment trials to use MCI in general or
12 perhaps the AD MCI group but, certainly, for drug treatments
13 that are designed to prevent the progression of the disease,
14 then the specificity of the disease I think is very
15 important.

16 DR. KATZ: Let's talk about symptomatic
17 treatments. The question is whether or not the grab-bag
18 that we want to call MCI is sufficiently similar across the
19 different underlying etiologies so that we can say this is a
20 treatment for MCI; it doesn't matter what the underlying
21 pathology is. Let's just talk about symptomatic. Do we
22 believe it is sufficiently describable across etiologies?
23 In other words, is the MCI of vascular etiology -- does that
24 look the same clinically as the MCI of Alzheimer's disease?
25 If we can answer that question, that has profound

1 implications for drug development.

2 DR. PENIX: I defer to the Alzheimer's treatment
3 people but, certainly, the key to the MCI diagnosis is the
4 memory impairment and I think that by focusing on the memory
5 impairment for symptom treatment, then you include all
6 patients with that memory impairment. But, again, I would
7 like to defer to some of the Alzheimer's experts.

8 DR. KAWAS: I would like to make a couple of
9 comments and then you can have the floor, Dr. DeKosky. Dr.
10 Katz gave us a couple of things to discuss that struck me,
11 as I was listening to everybody. He asked us is this just
12 early Alzheimer's disease? I don't think a single speaker
13 got up there today who within the first paragraph of their
14 talk did not essentially, in one way or another, say that
15 they thought this was early Alzheimer's disease. They used
16 terms like preclinical AD, prodromal AD, broadened to
17 prodromal dementia. The most broad we heard was that this
18 determines the risk set for development of Alzheimer's
19 disease, a high risk set.

20 I think most of us believe that probably MCI is
21 prodromal for insidious onset of dementias of all sorts.
22 Having said that, the most common insidious onset of
23 dementia by far is Alzheimer's disease. I think that, in
24 addition, we believe that some of the other dementias, like
25 vascular dementias, may have an initial insidious prodromal

1 something other than memory. So, perhaps Alzheimer's might
2 even be over-represented beyond proportional for MCI people.

3 But there is also not a single speaker today who
4 did not use the word heterogeneous, and the best I got out
5 of everybody when I asked specific questions was that they
6 thought we could identify homogeneous groups within this
7 heterogeneity. I think, in a sense, that is the answer to
8 your question. Most people right now commented that we
9 cannot tell apart MCI from vascular dementia or MCI from
10 Alzheimer's type, and that all of these things are
11 undoubtedly included in MCI. I am sure somebody feels I
12 took that to an extreme, so I want to give an opportunity to
13 the people at the table to comment, especially if they
14 disagree with some of the comments I just said. Dr.
15 Reisberg?

16 DR. REISBERG: I think it is very important, the
17 point you are raising. All these studies utilize -- if they
18 don't utilize it in terms of words, they are utilizing in
19 terms of procedures a diagnosis of, if you will, MCI of the
20 Alzheimer type. For example, all these studies are
21 excluding persons who have low B12. All these studies are
22 excluding people who have thyroid disturbances. All these
23 studies are excluding people who have nutritional
24 disturbances, anemia at a certain level, medical conditions,
25 hepatic conditions at a certain level. You know, if I walk

1 upstairs in my hospital, 50 percent of the patients have
2 symptomatology, both dementia and MCI, as a result of
3 various medical illnesses.

4 So, necessarily it has really been so routine that
5 it has been sub rosa, but all of these studies incorporate
6 those kinds of exclusions. The question is how rigorous one
7 wishes to be in these exclusions. Do you want to
8 incorporate a Hachinsky exclusion or not for vascular
9 dementia? Do you want to incorporate major symptomatology
10 of Lewy body dementia exclusions or not to try to exclude
11 MCI of the Lewy body type?

12 DR. CHUI: I would like to address your question,
13 Dr. Katz, about how reliable are these entities, how well
14 can we diagnose them. I would like to divide that question
15 into two separate sub-questions. One is how good is the
16 diagnosis for MCI for predictive validity, for predicting
17 that there is going to be a progressive decline? I think
18 from what I have heard today and what I believe is that it
19 is pretty good for that.

20 The second question is how good are we at dividing
21 the subtypes of MCI by different etiologies? And, I don't
22 think we are good at that. I would say that for the second
23 question, if we just turned it slightly and said how good
24 are we at defining dementia, we are pretty good. How good
25 are we at distinguishing the subtypes of dementia? We are

1 not very good.

2 So, if we just challenge ourselves a little bit
3 more and try to make these distinctions earlier for MCI,
4 just extrapolating, we would say that this is a little
5 harder. We are now pushing the edge. We are trying to
6 distinguish from normal aging. It is going to be a little
7 bit harder for us but now we have come ten, twenty years
8 beyond dementia and I think we can push the envelope for
9 predicting decline. But I still don't think we are very
10 good at predicting the etiologic subtypes. But I think we
11 have come along enough that we should recognize this as an
12 entity.

13 DR. WEINER: Dr. Katz, your question was whether
14 this is a symptom complex or whether one could view it
15 independent of what the underlying cause was. That was
16 really your question, as I understood it.

17 DR. KATZ: Well, if people believe that there are
18 many causes for MCI, even though there might be a
19 predominant one, early Alzheimer's, when we think about
20 writing labeling we have to think about whether or not we
21 can describe the condition for which the drug is going to be
22 indicated. So, if there are many different causes of MCI, I
23 have a fairly simple question, is all MCI MCI, at least from
24 a clinical point of view? Does it all pretty much look the
25 same regardless of the etiology. That would be a first step

1 at least in deciding how to develop drugs for it and how to
2 write labeling for it. That is my question.

3 DR. WEINER: Again, I don't work in the field but
4 I would think it would depend on the specific trial that was
5 done in the various populations, or whatever, that the
6 people wanted to have the drug used for. Again, I would
7 agree with the comment before that something that was for
8 symptomatic therapy might be different than something that
9 was for progression. You might also think that the
10 underlying substrate of mild cognitive impairment, or
11 whatever, is certainly in the hippocampus and you do have
12 these changes that you can see on imaging. But I think it
13 ultimately comes down to the drugs that are tested and what
14 the primary outcome measures are.

15 DR. TEMPLE: I think the history of these kinds of
16 difficulties is that you do the best you can, and that
17 sometimes things happen to enable you to distinguish things
18 that you formerly felt were the same better than you could
19 before. Sorry to use another cardiovascular example, but we
20 now know that heart failure comes in two flavors and that
21 the treatments are widely different depending on whether
22 your problem is the ventricular beat systolic function or
23 filling, diastolic function. And, the drugs that work in
24 one don't necessarily work in the other and might even be
25 adverse. But for decades people didn't realize this and all

1 of the above got included in clinical trials. That probably
2 decreased the effectiveness of certain treatments but since
3 we didn't know any better and the net effect was beneficial
4 the drugs were approved for undifferentiated heart failure.
5 Now that we are smarter we won't do that anymore.

6 So, the situation conceivably, I guess, could be
7 the same here. If the best you can do still isn't enough to
8 enable you to distinguish early Alzheimer's from early
9 multi-infarct dementia and you can't do any better than
10 that, you can put everybody who might be appropriate in the
11 trial, do your best to see if you can identify
12 characteristics that predict outcome but face the
13 possibility that you won't be able to do it very well, and
14 that a certain fraction of the people you put in might be
15 the wrong people. It wouldn't be the first time, and I am
16 sure some of the people in later Alzheimer's disease trials
17 really had something other than Alzheimer's disease. I
18 mean, it is hard to imagine that diagnostic accuracy was a
19 hundred percent.

20 DR. GRUNDMAN: I was actually going to make the
21 same comment. You know, I think the MCI of the AD variety,
22 it is not a perfect diagnosis but it is sort of the best we
23 can do, and I think we can, for the most part, differentiate
24 it from, say, a vascular etiology. You know, people who are
25 entered into these trials undergo CAT scans or MRIs

1 routinely to rule out evidence of stroke. So, we don't
2 think their cognitive impairment is due to stroke. As was
3 pointed out by Dr. Reisberg, they also undergo an extensive
4 laboratory battery so that it is not due to B12 or thyroid
5 disease or any other thing. So, it may not be a hundred
6 percent perfect but, you know, it is pretty good.

7 DR. DEKOSKY: There are a couple of different ways
8 you get there and, actually, I think I like the
9 cardiovascular analogy this time --

10 [Laughter]

11 There is one kind of MCI that I think most of us
12 who work in the field are pretty comfortable with, and that
13 is the amnesic disorder in isolation. I think the reason
14 for that is thinking anatomically about the pathophysiology.
15 There are a limited number of disorders that can give you an
16 isolated defect in short-term memory. There is Alzheimer's
17 disease in its early stages. There is hippocampal
18 sclerosis; the effects of someone who recovers from herpes
19 encephalitis who suffers medial temporal damage and people
20 who have an ischemia that gives them ischemic damage. If
21 they lose both hippocampi or the entorhinal hippocampal
22 system, humans end up with short-term memory deficits. If
23 you don't have both of those areas damaged -- if you have
24 visual and verbal delayed recall problems, for the most part
25 you have to have damage in those systems and there are only

1 a couple of disorders that can give you that.

2 I think that is why, in addition to the fact that
3 we can measure the volume of the hippocampus, that
4 particular pathway is the best trial pathway we have. The
5 problem is -- and it gets back to Claudia's comment -- that
6 we all started by saying this is a heterogenous disorder and
7 a bad term. The problem is that there are a couple of other
8 ways you can get to Alzheimer's disease that we discovered
9 on the way to looking at these earlier and earlier cases.

10 The group that consistently comes out looking very
11 much alike are the ones that are in this amnesic group and
12 I think there is a very strong anatomical underpinning for
13 that, either because of other disorders which are static and
14 which don't enter into this because most of the clinicians
15 will say, well, yes, this problem started after an attack of
16 encephalitis or after an acute event of syncope and
17 hypotension. It is the progressive ones. If you take that
18 group out and say here is a well-defined, well-tried pathway
19 that says that if you have amnesia progressing these are at
20 extraordinarily high risk to develop Alzheimer's disease
21 because there isn't much else that happens, with the
22 possible exception of hippocampal sclerosis, that can give
23 you that kind of clinical syndrome. The question is what is
24 the denominator of that group, the question that Dr.
25 Wolinsky asked earlier. We don't know yet. Now we will go

1 back and try to find that in our population studies.

2 The second question is what about these other
3 cases who actually go to Alzheimer's disease? They really
4 are a heterogeneous group. They usually come in with more
5 diffuse kinds of complaints. The two domains that are
6 impaired but neither one of them is really on the floor yet,
7 those are the ones where the question of Lewy body disorder
8 and especially the question of vascular disease may come in
9 that we are a lot less certain of.

10 To say that we have a pretty clear path of the
11 amnestic MCI to AD I think is probably -- I mean, I am
12 fairly confident of that one. I said I was surprised by our
13 own data that suggested -- although as Ranjan has pointed
14 out we are cleansed by having one of the specialty clinics,
15 clearly there is a pathway to Alzheimer's disease in that
16 group.

17 Parenthetically, I would say that although we are
18 not that good when we look at the autopsies at the Alzheimer
19 centers in terms of accuracy of diagnosis, but also those
20 2000 cases reflect the experience of people who were
21 diagnosed years ago who are part of our collective
22 experience. Even before we knew much about frontal temporal
23 dementia or Lewy body disorders or some of the other less
24 common ones, it is likely that if we start now I certainly
25 would hope that our accuracy would be better. We certainly

1 under-diagnosed FTD until it came to people's attention
2 during the course of being incorrect about our path.
3 diagnosis.

4 But, I think it is the second one that we have to
5 concentrate on, and I think if the question is, is all MCI
6 the same, in my view the answer is no. The term alone
7 brings in everything. Asking for a pain equivalent to that
8 I don't think makes sense. I would make every one of the
9 indications stand on its own two feet as far as saying this
10 works for an indication. I also don't have any allusions
11 that approval for one would result in people trying it for
12 all of the others, and in some cases they have had pragmatic
13 reason to try it because some of these, but not reliably and
14 regularly -- some of these other kinds of pathways also lead
15 to Alzheimer's disease and it may work for some of the other
16 pathophysiologies that simply haven't been tried yet.

17 DR. LEBER: I am Paul Leber and I probably have
18 numerous conflicts of interest but none that I think apply
19 here, but I do work at times with the regulated industry.

20 A couple of conceptual points that I haven't heard
21 and I wonder why I haven't. One is the distinction between
22 a maneuver used in the clinical trial setting in which to
23 produce an enriched sample where the likelihood of the
24 response is increased. That is one concept of MCI where MCI
25 is a shorthand notation for a maneuver which has its local

1 validity and use. I think the consortium study was based on
2 that idea. It has nothing to do with MCI per se, but it is
3 a way to get more endpoints within a short period of time
4 and a smaller sample.

5 The other is a broader question I have and it is
6 really for everyone here. We have been talking today as if
7 you really know what the predictive positive power of the
8 MCI diagnosis is. I would suggest that you may have
9 sensitivity and specificity but, because you haven't really
10 used the trial in a population, you really don't know what
11 its predictive power positive is when you have different
12 prevalences of people with various conditions there. Given
13 the epidemiological issue, it might in an enriched
14 population, say, in clinics which are specialty clinics and
15 have a very, very good predictive power and, yet, if you
16 move from that to the general population, perhaps just the
17 general practitioners or good old-fashioned psychiatrists
18 like myself, it might have a very different predictive
19 power. So, I think to get a single answer to this is sort
20 of like the average size of fruit. You can get one but I
21 don't know to what it applies.

22 DR. KAWAS: Thank you, Dr. Leber. I think the
23 point about predictive power in the population is a really
24 crucial one actually.

25 Keeping to the questions, we have actually sort of

1 been working with all of them but I want to focus us for the
2 moment on what outcome measures are appropriate for use in
3 clinical drug trials conducted in MCI. Here is a place
4 where probably there is the most difference of opinion from
5 the committee, at least as I heard it, where a fair number
6 of people felt that conversion to dementia or Alzheimer's
7 disease was the primary best outcome; others felt
8 symptomatic improvement or affecting the rate of decline or
9 change. So, would anyone on the committee like to start
10 commenting or discussing the outcome measures for MCI
11 studies? Dr. Grundman?

12 DR. GRUNDMAN: I think the thing we know most
13 clearly is that these people progress to Alzheimer's
14 disease. So, I think it has the most face validity and it
15 is the best thing we have to power these studies at this
16 point.

17 On the other hand, I think that obviously we want
18 to show that there are changes in cognitive impairment. So,
19 I think there should be a cognitive measure as well as a
20 neuropsychological battery which is sensitive, although at
21 this point I can't tell you which components of the
22 neuropsychological battery may show the most sensitivity to
23 change in these patients. That is something that we are
24 going to see over the course of the trial.

25 Obviously, we want to look at changes in function

1 so we need ADL scales. And, I think we need a measure of
2 clinical global impression, or at least a clinical measure
3 like the CDR or a clinical global impression depending on
4 the length of the study so that we can be sure, at least for
5 the shorter trials, that the changes that we are seeing are
6 clinically significant.

7 DR. KAWAS: So, in that list you just gave us the
8 primary outcome you are suggesting should be conversion to
9 dementia, and all the others are secondary outcomes?

10 DR. GRUNDMAN: Well, in the paradigm of a
11 prevention or a delay to Alzheimer's disease type clinical
12 trial which is what we based our study on for three years.
13 Now, in a shorter-term trial obviously you wouldn't be
14 looking at conversion to AD because you wouldn't be powered
15 sufficiently to do that, and in that sort of situation you
16 would be looking primarily at symptomatic improvement, in
17 which case measures of memory or cognitive and perhaps a
18 clinical global might suffice. But I think nobody really
19 knows whether or not there is going to be sufficient power
20 to see an effect in those short-term trials unless the agent
21 can either reverse the disease and actually result in some
22 sort of symptomatic improvements or has symptomatic benefit
23 on its own.

24 DR. PENIX: I will make a quick comment. I have a
25 problem with the conversion to AD outcome, that is, unless

1 it is used for prevention of progression of disease trial.
2 I am not clear what that means as far as a symptomatic
3 trial. It just means that you are delaying your clinician's
4 ability to make that diagnosis I think. So, I just have a
5 problem with that one for symptomatic treatment.

6 DR. GRUNDMAN: I think the idea is that we are
7 sort of presupposing that we actually know what the
8 mechanism of the drug is. So, I think what we are trying to
9 do here is look at progression to a clinical outcome, and I
10 think what we are trying to say is we don't know what the
11 mechanism -- we may have ideas about what the mechanism is
12 but, you know, even some of the symptomatic agents also
13 shown to have changes on amyloid processing, some of the
14 symptomatic drugs may actually have disease progression
15 aspects to them. So, you know, if we are dealing with a
16 trial over three years and we are looking at an outcome of
17 clinical dementia of the Alzheimer type, I don't think we
18 can say up front that we know whether or not we are dealing
19 with a symptomatic trial, we are dealing with a disease
20 progression trial. I think that what we are trying to do is
21 trying to get other biomarkers, evidence of change, that
22 would support one or the other but I think that the
23 importance of delaying a clinical entity such as dementia
24 stands on its own right, and also that the dementia, as I
25 pointed out before, has actually very good inter-rater

1 reliability between raters in diagnosing AD.

2 DR. KAWAS: Dr. Temple, Dr. Katz and then Dr.
3 DeKosky.

4 DR. TEMPLE: Apart from looking at physical
5 consequences of progression on MRI and things like that, or
6 CAT scan or whatever is appropriate, one could routinely ask
7 that any trial of this kind have a return to no therapy
8 component at the end, that is, where the placebo group
9 continues on and you observe the patients who have been
10 treated for a reasonable period -- I don't know what that
11 is; it might be eight weeks, to see if they persist in being
12 better off than the patients who were given placebo the
13 whole time. In drugs for Alzheimer's disease, at least if
14 you wait long enough, they have generally returned to be on
15 top of each other, indicating the treatment was symptomatic,
16 albeit long-lived, and not a fundamental change in the
17 disease.

18 I guess one might also ask for whether the groups'
19 deterioration curves diverge as opposed to remaining
20 parallel over the period of time as another possible
21 indicator of whether you are changing the fundamental nature
22 of the disease or not. But if progression to as the
23 specific endpoint is the goal, you can't really see if they
24 diverge because you are just going to reach the endpoint.
25 But the question then is should we ask that in any such

1 trial there be an off-therapy study added to it to help
2 define what you have actually done?

3 DR. GRUNDMAN: Well, in actuality it is very hard
4 to do that because, remember, the endpoint of the study is
5 dementia of the Alzheimer type so there is an ethical
6 mandate to treat these patients once you have made the
7 diagnosis. In fact, typically what happens is the patient
8 comes in and there is sort of a clamoring by the patient and
9 the physician. They think this person has now reached a
10 critical stage where they need to be treated. So, if you
11 were to start offering them placebo or off-stage at that
12 point in the trial it would be difficult to do. Now, in the
13 shorter-term trials it would make some sense to do that
14 because at that point they would still be MCI.

15 DR. TEMPLE: I presume that is because you know
16 you have changed the fundamental nature of their anatomy.
17 Otherwise, why would it be unethical to test the symptomatic
18 treatment? Why was it okay to take people of their
19 Alzheimer's disease treatment in trials of galantamine and
20 other things like that after many months of apparent
21 improvement? Why was that okay? I don't think we have
22 reached the point where we know that it is essential to gain
23 these small benefits.

24 DR. GRUNDMAN: I am just saying in practicality it
25 would be very difficult to do that type of placebo end to a

1 study where the endpoint is the development of Alzheimer's
2 disease.

3 DR. WOLINSKY: I think you put this very well, and
4 the issue is in the patient who hasn't met the study
5 endpoint, that is, has not progressed to the point of being
6 diagnosed, if this is a fundamental change in the disease
7 which moves slowly at MCI, would there be irreversible harm
8 to remove a drug from those who had not progressed for a
9 short interval of time, six to eight weeks, to find out if,
10 in fact, in an unusually short period of time they reverted
11 to dementia. Then, you would be able to reinstitute drug
12 therapy and if they reversed quickly find that this had been
13 cosmetic therapy and had not had a fundamental effect on the
14 disease.

15 I think this is a difficult issue but, again, it
16 comes down to the point of the difficulty of the ethics of
17 wanting to advance our understanding and treatment of
18 degenerative diseases versus our running from the
19 possibility of learning how to advance the therapy of
20 degenerative diseases.

21 DR. DEKOSKY: I want to get back to LaRoy's
22 initial question. Here is a potential outcome, let's make
23 the assumption that the medications do not affect the
24 fundamental progress of the disease, that is, they don't
25 have a biological effect. They are merely symptomatic. If

1 you were to do a typical treatment trial with these
2 medications you would use them in patients with clear-cut
3 probable AD and they have two domains, one of which is
4 memory. Now remove the other domain and now all you have
5 are people who have an isolated memory impairment and they
6 do not have significant impairment abnormalities in any
7 other cognitive domains. It is that domain that this
8 symptomatic medication is fighting to hold back from
9 emergence. That is the way I look at these trials.

10 If it turns out that you followed all of these
11 patients, as all the data shows that we do, then they fall
12 to AD when they drop on the Kaplan-Meier, they have
13 developed a second domain. They are already two standard
14 deviations down in amnesic disorder. The question is could
15 an esterase inhibitor or any other symptomatic drug hold
16 back the clinical manifestation of a language problem, a
17 visual-spatial problem and executive problem? As long as
18 they hold it back, it is not the clinician's impression
19 which is altered; as long as they hold it back, it is the
20 patient doing better.

21 So, that is the difficult crossover of this
22 clinical progression issue versus the substantive structural
23 reversal or structural holding steady of abnormalities. You
24 might even look at it as some variety of things which are
25 marching along but, if we just assume cholinesterases work

1 only on the cholinergic system, the cholinergic contribution
2 to the drop in the second domain is held back by the drug,
3 that second domain doesn't fall and a person remains just
4 amnesic. Thus, the interpretation of one of these trials
5 that uses AD as an endpoint demonstrates that that drug can
6 hold it back. That, I think, may be a better way to sort of
7 look at it but it is also the reason why when Dr. Katz asked
8 is there a global MCI pathway, probably not but one defined
9 pathway you can make the rationale for is why we do the
10 studies that we do, because we do have a rationale, even
11 with the symptomatic drugs, for looking to see whether it
12 will affect the emergence of the full-blown disease in these
13 cases.

14 DR. FELDMAN: Howard Feldman, from Vancouver. I
15 wanted to offer a comment on one or two things that have not
16 received the emphasis that I thought they were going to.

17 There has been a sanctity over the transition
18 point at which MCI becomes dementia. One of the questions
19 is that a lot hinges on functional assessment in moving from
20 a cognitive deficit into meeting criteria. That assessment
21 of functional deficit has been presented today as if it is a
22 fairly precise point and, in fact, it is a harder point than
23 any of the cognitive measures that are used as an outcome.
24 So, when one does a delay to conversion study and takes the
25 functional aspect on conversion I think there is a lot of

1 work and precision that needs to be given to that point
2 which doesn't currently exist. It has come up a little bit
3 earlier in relationship to things like is denial an
4 executive dysfunction? Is it interfering with day-to-day
5 function, and at what point will a high functioning
6 individual be called as having lost their functional
7 abilities?

8 So, that is one point I would like to comment on.
9 The other is that it has been assumed in the deliberations
10 today that, again, it is a very smooth process of transition
11 from MCI to dementia and nobody has commented on the
12 intercurrent events that will precipitate dementia being the
13 case. For example, the person who goes for surgery who has
14 MCI, who comes out of surgery and has had a step-wise
15 decrement now is demented and, yet, has had really an abrupt
16 episode of something that has occurred. Again, it goes
17 against this homogeneous, smoothly transitioning state from
18 one to another. I think where functional deficits have been
19 superimposed on top of some cognitive deficits but in a very
20 abrupt way, that goes a little bit against the flow of the
21 ways the paths have all been outlined.

22 DR. DEKOSKY: Two quick comments. The first is
23 that the second issue I think is a special case. We all see
24 these cases. But I don't think anybody implied that this is
25 a smooth transition. Smooth curves are not the same thing

1 as a smooth transition and people do go into AD change in
2 various ways, although I think we have asterisks by the
3 cases who have had something else happen -- an acute
4 disorder, a syncopal episode, mild trauma, stress that they
5 suddenly emerge from with worsened disorders. So, I don't
6 know that we have underestimated that. I think we are just
7 not quite sure how, other than by invoking the concept of
8 brain reserve, to deal with the pathophysiology.

9 Although the functional issue for us is the
10 paramount one, to reach ADRDA and NINCDS criteria for AD you
11 don't need to have a functional decline. So, in fact, I
12 believe -- and maybe Mike can clarify this for us -- you
13 could transition from MCI to probable AD without actually
14 losing function in the way most of these trials are defined,
15 although there are functional assessments that are done
16 serially.

17 DR. DUARA: I would like to both agree and
18 disagree with Dr. Feldman. I agree entirely with his thesis
19 that it is really difficult to define the transition. I
20 think it adds variability. The part I disagree with is that
21 he said nobody else had said that. I said that several
22 times this morning. So, in essence we agree a lot on those
23 points.

24 I think we should consider this as well, why does
25 it take twenty-two million dollars to do an MCI trial? The

1 main reason is because it has to go to three years where you
2 have enough power to look at conversion to dementia. That
3 is a very difficult endpoint to use because of that reason.
4 Wouldn't it be much simpler if we used cognitive measures of
5 change to look at the symptomatic effect of a drug on MCI?
6 And, maybe we could do the same sort of trials that we have
7 done with Alzheimer's disease.

8 The difficulty that I see is that we don't really
9 have at this point valid measures, or at least measures that
10 have been evaluated the way the ADAS-COG has been evaluated
11 in probable Alzheimer's disease. We don't have those kinds
12 of measures in MCI that have been validated that show a
13 gradual decline so that we can see that there is a change in
14 that path. There is a 7.0 decline in the ADAS-COG per year.
15 We don't know what the changes are in MCI and what measures
16 we should use. Probably the ADAS-COG is going to be a
17 useless instrument in MCI because it is not sensitive
18 enough. I don't know that for sure but I would expect it.

19 So, I think that one of our challenges is really
20 to look at all the instruments that have been used in the
21 various MCI trials and evaluate those instruments, and
22 perhaps come up with some additional instruments that can
23 actually measure this change that I think must be occurring
24 in response to treatment if these people have very early
25 Alzheimer's disease.

1 DR. KAWAS: You mean memory instruments?

2 DR. DUARA: Yes.

3 DR. KAWAS: Or, do you think other areas of
4 cognitive will have to be developed also?

5 DR. DUARA: Well, I think they can be primarily
6 memory instruments but they could include a variety of
7 others -- language, for example. We know that naming
8 disorders occur very commonly in Alzheimer's disease and so
9 tests of naming and other tests would be useful as well.

10 DR. OLIN: Yes, I am Dave Olin. I am a
11 psychiatrist from Bloomfield, Michigan, so I am from the
12 real world and I have a real-world issue or problem to bring
13 up that bears on what you all are talking about and I would
14 like you to consider it. A couple of months ago a friend, a
15 physician, came with mild memory complaints. He had heard
16 of MCI and we did a workup with neuropsych testing, got the
17 CDLT and the Waxler Logical Memory Subscale, and he
18 qualified for all the Petersen criteria. So, we talked it
19 over and he wanted to start Aricept, and it seemed like a
20 reasonable thing and I gave him a prescription. The next
21 day I got a call from the benefits manager of his insurance
22 company saying, "does the man have Alzheimer's?" I thought
23 about it and I said no. "Well, we only prescribe
24 cholinesterase inhibitors for Alzheimer's." So, I thought
25 about it some more and I said, "how about amnestic

1 disorder?" "No, I never heard of that but, no, it is not
2 going to work."

3 DR. KAWAS: Did you ask him how about the earliest
4 of Alzheimer's?

5 DR. OLIN: Yes. Well, being a physician, he is
6 going to get samples but I am going to have problems with my
7 other patients.

8 DR. KAWAS: Actually, I think this brings up an
9 important point. Although we have touched today on the
10 difference it makes to patients what we call this, and I
11 don't think that is to be minimized, it also makes
12 differences to the healthcare system and it makes
13 differences to the legal system. I recently moved to
14 California, and in California physicians are obligated to
15 report Alzheimer's disease and dementia diagnoses to the
16 state for the driver's license, but they are not obligated
17 to report MCI. So, in fact, it is a very thin line that we
18 are walking and it doesn't just affect the patients'
19 feelings what we call this. It is going to have
20 ramifications well beyond that. I think we need to keep
21 that in mind.

22 DR. GRUNDMAN: I think that was really an
23 excellent comment. From a real-world physician point of
24 view, they are not going to call these patients AD. They
25 are just simply not. These are not AD patients, clinical AD

1 patients. If we are going to try to get them therapy, then
2 what we need to do is we need to do studies in patients who
3 have MCI and validated that they actually do something in
4 patients with MCI, and then approve them for patients who
5 have MCI.

6 DR. KAWAS: We have done a fairly good job of
7 going through the majority of the questions. The final one,
8 should clinical drug trials in MCI incorporate any special
9 features in their design, was brought up sort of
10 tangentially in some of the comments and specifically by Dr.
11 Temple who asked us about withdrawal designs or randomized
12 start designs. But are there any other comments people on
13 the panel would like to make about special features that
14 maybe should be considered for drug trials in MCI?

15 [No response]

16 Is there anybody who would like to say anything
17 then before we summarize this meeting? Have we answered any
18 of the questions, if not all of the questions, that the FDA
19 has posed to us, Dr. Katz?

20 DR. KATZ: Well, we will have to go over the
21 transcript. Just to go back to question four about outcome
22 measures, obviously, a lot of people have been talking about
23 time to the diagnosis of AD, but certainly comments have
24 been made about looking at the symptoms of MCI, the memory
25 symptoms.

1 Just to remind everyone, obviously for symptomatic
2 treatments for Alzheimer's disease currently, the
3 requirement is that there be an effect on a cognitive
4 measure but also on a global measure to ensure that that
5 cognitive improvement actually has some clinical meaning.
6 So, I would just ask that question. If looking at the
7 symptoms of MCI is how trials will be designed, does it make
8 sense to also require that there be some sort of measure of
9 global functioning to ensure that you are actually making a
10 difference to the patient, in other words, this sort of dual
11 outcome that we require for Alzheimer's?

12 DR. VAN BELLE: I was going to make one comment
13 about the fourth question. We have kind of a laundry list
14 of outcomes and the pharmaceutical firms are going to want
15 to know if we have any kind of ordering of them because
16 there is just no way that they are going to look all of
17 them, and the FDA will not allow them to sort of say any one
18 of the above we will use for clinical efficacy. So, I think
19 this group should come to some ordering, and I think we have
20 heard a little bit of an ordering already.

21 While I have the floor, I have one other question
22 going back to the first question about can MCI be defined.
23 I don't think that this group has really come up with a set
24 of criteria. I know that we have looked at Ron Petersen's
25 list, which I think we all have nodding agreement to, but I

1 think it would be very helpful for the audience and for the
2 FDA to really come up with a list that would say we would at
3 least like to see these features with MCI. I think that
4 would be helpful for them so that they can go on and do
5 their clinical trials with the appropriate groups.

6 DR. KAWAS: If I understood, you just gave a
7 challenge to the committee to come up with the list of
8 features for MCI that --

9 DR. VAN BELLE: Two challenges. One challenge is
10 in terms of the endpoints. I think we should advise the
11 FDA, if possible, on some kind of a ranking of all these
12 outcomes. Five or six groups of outcomes just is not very
13 helpful. It basically is a laundry list, and can a
14 pharmaceutical firm pick any one of these, or must they pick
15 at least one? Russ mentioned at least looking at some sort
16 of global outcome. Well, what exactly would the FDA like to
17 see in terms of the ordering of these outcomes?

18 Secondly, almost going back to the beginning, what
19 are the criteria for outcomes of impairment that we can
20 advocate?

21 DR. KATZ: Yes, as far as the outcomes, again, it
22 would be great I suppose if everybody endorsed a particular
23 scale in these patients and said, yes, you have to do this
24 for looking at the symptoms type of an outcome. I don't
25 expect that this group will be able to do that. If you can,

1 great. But assuming that you can't do that, I am more
2 interested I suppose in sort of domains of interest that
3 ought to be assessed, again, drawing from the Alzheimer's
4 analogy where we require an outcome looking at cognitive,
5 which is of the core symptoms, and a global. I am just
6 wondering whether or not, if this symptom approach is
7 adopted, that same sort of philosophy should apply.

8 DR. KAWAS: I would actually like to take a stab
9 at a comment on that. I find the outcome of conversion to
10 dementia very appealing in a large number of ways. However,
11 I find no appeal to it at all for a symptomatic trial. I
12 don't understand why anyone would want to do a trial that
13 would take three to five years to look at symptoms when they
14 could take a trial that would take one or, at most, two
15 years to look at symptoms.

16 So, if a symptomatic trial were being done I would
17 suggest that it should keep with the model that we are used
18 to in Alzheimer's disease, which is looking at cognition in
19 some objective way and a global measure of some sort just to
20 ensure that whatever cognitive change we measure with the
21 objective measure, in fact, does appear to have at least
22 some semblance of clinical impact.

23 DR. KATZ: Fine. Keep in mind that at least by
24 some definitions of MCI there is no functional impairment
25 other than memory. What I am trying to draw as an analogy

1 where everybody with Alzheimer's disease has a cognitive
2 deficit and they have a global dysfunction so you can
3 measure both. You can require that both be measured. At
4 least by some definition as I understand the Petersen
5 criteria, there really is no functional impairment. Other
6 people have different definitions of MCI that do include
7 functional impairment. So, you know, we are sort of back to
8 do we all know what we are talking about when we say MCI.

9 DR. TEMPLE: Suppose you looked in that case at
10 both the measured impairment and the patient's sense that
11 there is an impairment as two rather independent views of
12 the same thing? In other words, a sort of patient global
13 with respect to the impairment they came in with and the
14 ability to measure it. Not quite clinical global but maybe
15 not far.

16 DR. KATZ: Right, although, as you say, it is sort
17 of two independent looks at the same phenomenon. If a
18 patient's memory is improved, presumably they can tell and
19 you can objectively tell. It doesn't really ensure that
20 change in memory had some clinical utility, made them
21 function better.

22 DR. TEMPLE: Well, I think the patient's own
23 complaint is at least moderately credible although, as
24 people pointed out, if you get worse you may complain less
25 too.

1 DR. PENIX: If you do adopt that strategy, I would
2 recommend maybe the caregiver giving the caregiver input.

3 DR. KAWAS: And, what would you recommend when
4 there isn't a caregiver, which happens a lot in the real
5 world?

6 DR. DEKOSKY: You don't get in the trials.

7 DR. PENIX: That is a difficulty I think.

8 DR. REISBERG: Let me comment a little bit on the
9 functional element here. You know, I think it is a shame
10 that Ron isn't here to comment on this. I think we run into
11 semantics again, and when Ron says there is no functional
12 impairment I think he is speaking about functional
13 impairment in basic ADLs. There are many different
14 functional levels and I think he were here, despite the
15 criteria he would acknowledge that there are functional
16 impairments which are of a more subtle nature which occur in
17 MCI. Those functional impairments are, for example,
18 embedded in the global scales, be they the CDR, the GDS.
19 They are also present in the functional measures which are
20 used, if not universally, certainly occasionally in MCI
21 trials -- the ADCS functional measure and other functional
22 measures which can measure functional decline also in these
23 patients.

24 DR. DUARA: I think actually I disagree with Dr.
25 Reisberg. I think that Ron Petersen actually does exclude

1 people with instrumental activities of daily living
2 impairment for the most part. It is not clear to me that
3 they are all excluded but in general if they can't handle
4 finances and they can't do things clearly that they were
5 able to do before that are not basic ADLs, that are
6 instrumental ADLs, then they would be excluded from the
7 studies.

8 So, I think the question asked by Dr. Katz is very
9 relevant here in terms of what else do we look at besides
10 cognitive and I think we should have some sort of a clinical
11 global impression of change that could be assessed just by
12 talking to the patient. But I think there are also
13 objective measures of function that have been developed. A
14 colleague of mine, Dr. Lowenstein, has an objective scale
15 for evaluating functional impairment. Now, you might argue
16 and say, well, how is that different really from a cognitive
17 test? Well, it looks at specific functions such as doing
18 specific types of calculations that you would need to do in
19 a grocery store, and so forth. And, this has been a
20 validated test. So, I think one could use such instruments
21 as well as a so-called pure cognitive instrument to add
22 validity to the study.

23 DR. DEKOSKY: I think if we stick with the
24 criteria -- I am not sure how else to describe the criteria
25 for the one type that we have felt has had the most

1 consistent outcomes, which is the amnestic disorder, most of
2 the functional impairments measured have been very slight.
3 In a sense, it is a bit like a lot of the behavioral
4 assessment retrospective looks in the cholinesterase
5 inhibitors in Alzheimer's disease where it looks like there
6 is a signal that there is some improvement in behavior but
7 the levels of abnormal behaviors in those cases are so low
8 that it is very hard to see much of an effect. It would be
9 very difficult, I think, if we stuck to the current
10 virtually no functional impairment even in instrumentals --
11 Barry is right, if you dig deep enough you can find some but
12 in general the functional impairments are so low that
13 whether you could see a signal that would change I would
14 have a lot of doubts about, basically because these patients
15 don't have that degree of impairment.

16 Now, you might design a study to say they must
17 have a memory impairment and they must have some definable
18 functional impairment, but you could use as another marker a
19 pragmatic marker. But, for the most part, the pure memory
20 loss cases that we have had don't have all that much of a
21 problem in whether or not you can see reliable differences
22 in that group I have concerns about.

23 DR. SCHNEIDER: I am Lon Schneider, from Los
24 Angeles. I thought, Claudia, that other people would pick
25 up on your comment -- this concerns special features of

1 designs, that they would pick up on your comment that
2 although survival analyses or time to certain milestones are
3 attractive in some ways, in other ways they are very
4 unattractive. For instance, in these kinds of studies where
5 you are identifying people with a mild cognitive impairment,
6 as Steve Ferris would say, of the Alzheimer's type where
7 perhaps eighty percent of patients will develop at least
8 probable Alzheimer's disease in a few years patients are
9 being exposed to drug or placebo for long periods of time,
10 one, two and three years. During that time changes are
11 occurring. Their cognitive function, their behavior is
12 changing over time. Ignoring that or only looking at the
13 time to survival, you know, you ignore all this important
14 information on what the medications might actually be doing
15 over the interim. Then, afterwards when you hit that
16 endpoint, the endpoint of dementia is not the same as the
17 endpoint of death. There is life after dementia. Patients
18 are continuing with their illness. They are still on
19 medication or they may be switched to placebo and we know
20 very little about the effects of medication after that
21 point. Lastly, there are side effects. There are people
22 dropping out of these studies over the course of one, two
23 and three years that may create some considerable issue in
24 the accurate statistical analysis or in the statistical
25 interpretation if you just look at survival.

1 DR. WOLINSKY: Just an issue at least in the
2 conditions that I deal with and I think about a lot is how
3 to make more interesting drug trials than the ones we
4 currently have, and it sounds like when we are listening to
5 this issue of testing drugs for their ability to retard
6 progression to a later stage of Alzheimer's disease, and
7 also thinking about the issue of symptomatic treatment, one
8 wonders if an appropriate trial design would be one in which
9 you look early for symptomatic relief and late for
10 progression of disease. There would be, I think, some
11 rather attractive features to that kind of a trial from the
12 pharmaceutical industry who gets to learn something about
13 whether they have at least a base hit before they learn
14 whether or not they have a home run, since few of us hit
15 home runs.

16 DR. GRUNDMAN: I would like to point out that I
17 basically agree with what Lon said. Obviously, you know, if
18 we could determine that a drug was affecting the disease
19 process before they developed dementia we would do shorter
20 trials. We picked the term dementia criterion simply
21 because that was based on power calculations. Now, if it
22 turns out that after a year's time we can detect a 45
23 percent worsening on the CGIC, which may be a more sensitive
24 instrument than making a diagnosis of Alzheimer's disease,
25 then we may be able to move to shorter trials, and then the

1 issue of whether symptomatic or disease progression comes
2 up, we will have to deal with that on that level. But, it
3 may be possible to do shorter trials and look for biomarkers
4 or changes in MRI to try to sort that out.

5 So, I wouldn't say that dementia of the Alzheimer
6 type will be the trial design forever. I think it is just a
7 matter of we need to get more information about this
8 population cohort and to find out what types of measures are
9 going to be sensitive to respond in this population and what
10 moves and what doesn't move. I think until now we haven't
11 really had that information.

12 DR. DEKOSKY: Just a brief comment. In the
13 question about what other things should be done, most of
14 this discussion is centering upon what particular cognitive
15 tests or cognitive evaluations should be done, extrapolating
16 to people out in the real world. This bespeaks the need for
17 some kind of biological marker for us to be able to use in a
18 much more easy fashion than the generally careful and time-
19 consuming and unreimbursed cognitive assessments of patients
20 which are done in late life. It not only would make life
21 much easier and, in fact, make diagnoses more realistic, it
22 would stop a lot of the evaluation of people for whom going
23 down the path of a drug for a specific disorder wasn't
24 necessary because they clearly did not have the biomarker
25 associated with it.

1 DR. KAWAS: My only comment before I turn the
2 floor over to Dr. Katz is let's not hold our breath.

3 DR. KATZ: I want to ask a question that is not on
4 the list but it sort of incorporates all the questions, and
5 it is just basically the global question of do we think that
6 we are at the point in our understanding of MCI, even in MCI
7 of the Alzheimer's type if that is what we want to call it,
8 where we are ready to embark upon drug development and
9 approval? Do we know enough about, as Paul Leber talked
10 about, the positive predictive value in terms of do we have
11 diagnostic criteria that when we open it up to all
12 prescribers, all-comers, that they can be reliably applied
13 and they can identify these patients reliably? I mean, is
14 it ready for prime time in essence? I would be interested
15 to know what people think.

16 DR. KAWAS: Who would like to start with that
17 challenge? Dr. Penix?

18 DR. PENIX: Yes, a very simple study I would like
19 to see is whether there is reproducibility of either a
20 cognitive scale performed in a specialized Alzheimer's
21 disease or dementia setting compared to primary care
22 physicians. I think it would be very useful to see whether
23 we can transfer these instruments into a practical, everyday
24 setting. I would just like to see that just to see if it is
25 going to be possible.

1 DR. KATZ: Before a drug could be approved on the
2 basis of some of these studies?

3 DR. PENIX: I think it would help solve some of
4 the questions from my standpoint. This is my opinion, I
5 think it would help me feel that the primary practitioner,
6 the general practitioner in a very busy practice really has
7 a firm grasp on the concept of MCI and the ability to
8 diagnose these patients.

9 DR. TEMPLE: Would one say to do that would be to
10 do the first important trial in a population well defined by
11 experts and then try to mount a second trial that was used
12 in less technically sophisticated environments? DR. KAWAS: I
13 think you got a lot of nods around the table for that one.
14 Yes, we like your ideas.

15 DR. KATZ: That is fine, but I want to understand
16 whether or not people think that is necessary. They nodded
17 that they thought it was a good idea. That is not the same
18 thing -- I don't know why they nodded. That is why I am
19 asking.

20 DR. KAWAS: I saw everybody nod, so start
21 explaining. I saw the nods on that side of the table.

22 DR. DUARA: I think we are going to be in a
23 parallel situation with SSRIs for depression. I think that
24 many general practitioners now can diagnose overt
25 depression, major depressive disorder. They may not be that

1 good at diagnosing some of the dysthymic disorders and so
2 forth. Is it dangerous to allow a drug into the market for
3 a diagnosis that is less than Alzheimer's disease? I think
4 it is going to be overused, yes. I think that a lot of
5 people who are in the purely subjective memory, the "worried
6 well" category -- not a lot but some people are going to end
7 up on this drug. If that is the concern, I think we ought
8 to be overt about it. That is going to happen for sure.

9 But, is it important for us? If you look at the
10 balance of the situation, how commonly do we see mild
11 cognitive impairment? Are most physicians who deal with
12 dementia comfortable with diagnosing mild cognitive
13 impairment? I have no doubt that they are. I mean,
14 everybody that I talk to, colleagues of mine in this area
15 seem to have no problem with it and in general feel that it
16 is overdue. So, I think that coming to some sort of
17 consensus about that would not be a problem. Whether it
18 will be abused, I would agree with that too.

19 DR. KAWAS: Do you think the abuse or overuse
20 potential would change if the indication, rather than being
21 MCI, was something else like early Alzheimer's disease?

22 DR. DUARA: Possibly. I am not sure about that.
23 You know, people use drugs in an off-label sense a lot. So,
24 I think if we are talking about abuse they are not going to
25 say, well, you have early Alzheimer's disease, therefore I

1 am prescribing this medication. They are just going to say,
2 well, I think this drug might help you. Actually, I retract
3 that. I don't think it will make any difference.

4 DR. KAWAS: You don't?

5 DR. DUARA: No.

6 DR. KAWAS: Dr. DeKosky, you were nodding when Dr.
7 Temple suggested the design. Do you want to tell Dr. Katz
8 why you liked it?

9 DR. DEKOSKY: I think that is what is going on
10 now. I mean, I think those are the start of those. As far
11 as primary care physicians are concerned, I guess the
12 physicians in south Florida -- we have almost as many old
13 people but our physicians in the community tell us they
14 don't want to make this diagnosis. They don't want to make
15 an Alzheimer's diagnosis which we think is much easier.
16 Unless we come up with a very quick way, as Dr. Penix was
17 suggesting, for finding, for example, isolated memory loss
18 in the absence of other problems, a very easy way, the
19 physicians will continue, I believe, in large numbers to not
20 make the diagnosis for a variety of reasons. Some honestly
21 believe that it is normal aging. Others can't or don't want
22 to take the time because it is not reimbursed and they only
23 have so much time to see their patients. So, I think
24 depending on how much publicity it gets, they may well
25 decide that they will use this on these people who otherwise

1 they don't take a very careful look at. That is why I think
2 the sequence of designs and maybe even one primary design is
3 probably something we have to pursue.

4 I also feel a little bit strange. I don't know if
5 this is an issue that has come before this group before. We
6 are really talking about the designs of trials for a drug
7 which we do believe is symptomatic, whereas, if we knew that
8 there were three or four medications which we actually
9 thought were intervening in some specific structural or
10 mechanistic way in the disease we probably would be focused
11 a little bit differently on the nature of the trials that we
12 would do.

13 DR. WEINER: I just want to address Dr. Katz'
14 question of whether he thinks it is ready for prime time, to
15 use your words. I think the answer is yes. I think we know
16 enough about it. I think there are ways to measure it. I
17 think it is a very important area in the future as new drugs
18 become available. So, I think it is ready for prime time
19 drug development.

20 In terms of the drugs being used or being abused
21 or being prescribed perhaps not in the right situation, as
22 other people have said, I think this is common for all the
23 drugs we have and you are more concerned depending upon how
24 potentially toxic the drugs are. If it is a drug that may
25 be of benefit and has minimal side effects, one would be a

1 little less concerned about it. If it has more potential
2 side effects, then the labeling, or whatever, could be
3 adjusted appropriately. But I would answer your question
4 that I do think it is ready.

5 DR. WOLINSKY: I think Howard said it. To me, the
6 issue is risk-benefit in the end. There is no way to reject
7 in advance whether we should or shouldn't be making a
8 decision about when a drug is ready to go out into the
9 general marketplace until we understand this. So, if the
10 first study makes it clear that there is good benefit and
11 low risk, then there shouldn't be too many restrictions on
12 the access to the drug and, of course, it will be used more
13 broadly than was indicated. But if it comes in and says
14 that the benefit is marginal and the risks are high, if it
15 is let out at all it has to be let out in a way that puts
16 considerable concern on the physician's part about using it
17 unless he is sure about what he is doing, or she is sure
18 what she is doing.

19 DR. KAWAS: And, what if the most likely scenario
20 which is not if it is positive most likely, which is if the
21 benefits are modest or moderate and the risks are at least
22 moderate?

23 DR. WOLINSKY: So, if it is vitamin E, does this
24 matter?

25 DR. KAWAS: I think I am not quick enough at this

1 hour to understand that.

2 DR. WOLINSKY: No, I thought I saw one of the
3 trials where vitamin E was potentially one of the active
4 parameters, and that would mean probably this committee will
5 never look at it and Russ will never be able to control it.

6 DR. KAWAS: Let me tell you another secret,
7 neither will all the industry people sitting out there.
8 Most of the things that people are going to suggest are
9 going to be novel compounds, not vitamin E.

10 DR. WOLINSKY: But then, again, I think the issue
11 is going to be the risk-benefit ratio that we see when we
12 see the data that tells us that there is some efficacy here.

13 DR. KAWAS: So, if the benefit is moderate and the
14 risk is moderate, does that change in any way what we want
15 to tell the FDA about the indication being MCI versus
16 anything else?

17 DR. WOLINSKY: No.

18 DR. WEINER: What you did is, you asked what if it
19 is grey. That is basically what you said.

20 DR. KAWAS: Right.

21 DR. WEINER: So, then it is how grey is it? But
22 it is a valid question. What if it is on the fence? That
23 is basically what you asked. Because if there is a good
24 benefit and little risk, it is easy. If there is a great
25 risk and little benefit, it is easy. So, your question is

1 what if it is in the grey area. Then, that depends on the
2 individual case and it is hard to answer that directly but
3 that wouldn't stop me, in my own thinking of trying to
4 develop drugs or trying to find them.

5 DR. DEKOSKY: [Not at microphone; inaudible]

6 DR. KATZ: Can I answer that?

7 DR. KAWAS: Please do.

8 DR. KATZ: The answer is I don't think I want to
9 answer it.

10 [Laughter]

11 I don't think we are going to solve the question
12 of what if we have a reasonably good drug that is fairly
13 toxic. There is an infinite number of possibilities. You
14 couldn't possibly those questions here. The question I
15 asked was a methodologic one or a standards one. Do we have
16 the standards in place now to be able to say we can study
17 this thing or some subset of it, describe the patients so
18 that the typical practitioner will be able to reliably
19 identify those patients, and have outcomes that we think are
20 valid and are clinically meaningful? That is really the
21 question. Do we have research criteria here only in the
22 year 2001, or do we have sufficiently well-developed
23 diagnostic criteria and measurement systems so that we are
24 ready to approve a drug on the basis of what methodology
25 exists now and the knowledge that exists now? That is the

1 question I am asking.

2 DR. KAWAS: I am going to let the committee
3 comment for themselves but I think some of the answer that I
4 am hearing is that we feel like overall we have a lot of the
5 methods but they are restricted right now to the research
6 community, and there would be a significant but doable
7 translation necessary to get it out into the clinical
8 community. Is that in keeping with what a lot of the people
9 are saying?

10 DR. KATZ: And would a study in that, as Bob had
11 suggested, as an example, be necessary? Do we need more
12 work? I mean, you can't approve a drug -- I suppose you
13 could but we wouldn't expect to approve a drug for this
14 indication simply for the experts to use. But the question
15 is do we know enough now about it? Can we describe it well
16 enough now to be able to say that this is something, if we
17 do two studies and they are positive, that should be
18 available? That is the question.

19 DR. KAWAS: Everyone is looking at me except Dr.
20 Grundman. So, he can answer after I say I think that --
21 actually, I am going to defer.

22 DR. GRUNDMAN: The answer to your question is yes,
23 I think we do have criteria in place which are primarily
24 clinical. They have to have a memory impairment which is
25 corroborated by someone that they know who is close to them,

1 and it should be progressive. They shouldn't have evidence
2 of other neurologic disorders. I think the critical
3 question really has to do with the cognitive testing. The
4 question is whether or not there is an objective impairment
5 of their exam, and I think that for the purposes of our
6 trials we have fairly stringent criteria because we need to
7 make sure that we are going to get the number of endpoints
8 in the trials that we need to show some benefit.

9 But I think in the general community, if it is
10 going to boil down to what was mentioned earlier, which is
11 what is the risk-benefit in this population, clearly these
12 patients have a clinical disorder. I think Dr. Reisberg
13 pointed out, you know, these people with GDS 3s or CDR 0.5s
14 -- these are clinical scales that can be used in the
15 community by clinicians to try to grade the patients that
16 they are seeing in the trials. Then, all they really need
17 to do is to decide whether or not they think the impairment
18 is objective or not. If they can make that decision, which
19 is basically a clinical decision based on memory testing
20 that they are doing in their environment, I think that
21 basically this is a generalizable study to the community.

22 DR. KAWAS: I actually would disagree to some
23 extent. I mean, the CDR and the GDS, they sound really like
24 nice little instruments, 10-point scales, 4-point scales,
25 whatever. Those of us who work in the field, and Mike is a

1 leader of that, know that when we first tried doing the CDR
2 in these studies it took hours of training, hours of
3 vignettes. We would sit in a room and I think shock
4 ourselves at the difference in the way we were scoring
5 people, particularly around the 0.5 area, which is exactly
6 what we are talking about here. The GDS only complicates
7 that by giving you 10 points to choose from and zeroing in
8 on a 3 is not that easy.

9 So, no, the reason why I was nodding my head over
10 Dr. Temple's suggestion of two studies, the second one being
11 done in the community, is because I think that would be
12 almost the necessary test to show that it could be done in
13 the community. So, we would do the first round the way we
14 always do in clinical trials and with our usual expertise.
15 And, if we can find effect, then the second study, in
16 effect, would be to see if we could duplicate the effort
17 using community physicians in some other more simplified,
18 presumably, way to define them. So, that is why I was
19 nodding my head at your suggestion. I think we have the
20 obligation to show that it can be done in the community on
21 some level and that would be an excellent way to do it.

22 DR. DEKOSKY: We chose not to use the CDR even in
23 the study overseen by experts in the prevention trial
24 because is it so dependent on the caregiver -- leave out the
25 issue of how good the doc would be in making the call about

1 what the caregiver says, that is not going to be an
2 effective way of doing this in the community. The CDR is
3 very good in extraordinarily skilled hands. John Morris'
4 paper, coming out, I think gives credence to that, but it
5 won't be generalizable. I think we are into memory
6 checklists and some kind of brief memory test, and then a
7 memory checklist for function with the caregiver, the person
8 who brings someone in. At least to try to bring this to
9 some kind of very pragmatic but real use in the community,
10 it probably is going to have to come down to something like
11 that, otherwise we can continue to do what people would do
12 if there was a question, which is to send people to a
13 neuropsychologist which is not going to be the mainstream
14 way we deal with all these cases.

15 DR. KAWAS: I would even like to point out that
16 the CDR, which was a one-page instrument when it was
17 developed, is now a 30-page and about 30-minute interview
18 that has been structured and it takes a long time. That was
19 necessary only so that the experts could get on the same
20 page with it. So, it is not something that will translate
21 easily into the community. Dr. Reisberg?

22 DR. REISBERG: I would just feel negligent if I
23 didn't speak up about what I feel I know about. What we did
24 with the GDS was we took the 7-point scale that you had,
25 basically in terms of severity, already from the CGI, for

1 example. You had no impairment, very mild, mild, moderate,
2 moderately severe and severe. What we did was give that
3 clinical words, and those words have been extensively
4 validated, and I won't go into all the details here, but the
5 best validation was a study that John Overall did where he
6 actually queried spouses as to the presence or absence of
7 symptoms and, using principal components analysis,
8 reconstructed the scale based on 30 phrases from the GDS,
9 and reconstructed this scale. So, it is a very clinically
10 meaningful scale and clinically valid scale.

11 Now, there have been five different reliability
12 studies in the literature that I am aware of, and they have
13 been reliability studies at all different levels in all
14 kinds of different settings, from nursing homes to
15 university of Pennsylvania to chronic disease hospitals.
16 The reliability has generally been just approximately the
17 same as the Mini-Mental, about a 0.92 reliability
18 coefficient. So, you know, at least from everything that I
19 am aware of, that this is a reliable scale but, obviously,
20 one has to use it and it is subject to abuse if one doesn't
21 use it. So, if you check off boxes without reading the
22 words, then certainly it is subject to abuse.

23 DR. DUARA: In response to Dr. Katz' question, I
24 just want to point out that when the NINCDS criteria for
25 Alzheimer's disease were developed -- you know, we all know

1 what those criteria are. They require that you diagnose
2 dementia and that dementia be corroborated by a Mini-Mental
3 score plus other confirmatory psychological cognitive tests.
4 So, when tacrine was approved and then all the drugs after
5 that, the question is, is the general practitioner doing all
6 that to confirm a diagnosis of Alzheimer's disease? Is the
7 neurologist or the psychiatrist doing that?

8 We have a Florida brain bank so I get all the
9 medical records for everybody that dies -- not everybody but
10 those who donate their brain in Florida, and I look at all
11 the clinical reports. From neurologists, I would say ten
12 percent would do a Mini-Mental. Most of these patients have
13 never had any neuropsychological evaluations, not even a
14 Mini-Mental status.

15 So, are we applying an unreasonable standard, is
16 my question, to mild cognitive impairment when we are
17 saying, well, do you have well-defined standards? I think
18 in the research community for people who are dementologists,
19 if you will, you can diagnose that condition very reliably.
20 The reliability in the hands of the general practitioner is
21 going to be about the same reliability as it is for
22 Alzheimer's disease.

23 DR. KATZ: I suppose that is part of the question,
24 is that true? I mean, even though people can misdiagnose
25 Alzheimer's or at least don't apply the standard criteria,

1 at the time that all the Alzheimer's drugs were approved,
2 even the first one, those criteria were formalized. They
3 were an accepted diagnostic algorithm or set of diagnostic
4 criteria. That is not the case with MCI but I think we are
5 at an earlier stage of maturity, if you will, of the
6 diagnostic criteria. So, that is why I am asking the
7 question, besides the fact that for mild cognitive
8 impairment it might very well affect the risk-benefit ratio
9 in a different way so you really want to make sure that
10 people can accurately diagnose it.

11 Maybe when it is approved they won't. We have no
12 control over that, of course, as you say, but you want to
13 make sure at least by the time you approve a drug that
14 people can do it. Whether they do, it is beyond our
15 control, as I say. So, I think we are at a much earlier
16 stage here. So, that is why I am pressing the point. It
17 isn't as widely accepted as the NINCDS/ADRDA criteria for
18 Alzheimer's. So, that is why we are here.

19 DR. KAWAS: I am still hovering over the notion
20 that we might have a shot at getting out of here by five
21 o'clock. Dr. Shah, in a second I will give you an
22 opportunity to speak but mostly after that I would like Dr.
23 Temple and Dr. Katz to tell us where they would like this
24 committee to go from here for them. So, Dr. Shah?

25 DR. SHAH: I agree with Dr. Katz and Dr. Duara. I

1 just want to give a broader perspective for primary care
2 physicians. On an average, only 15-20 percent of everything
3 we have recommended as standard screening tests have been
4 performed, meaning hormone replacement therapy is 15 percent
5 by obstetricians and family practitioners. Mini-Mental
6 State Exam by internists was around 17 percent for memory
7 complaints. The screening for colon cancer, screening for
8 everything else which is proven beyond doubt is not more
9 than 20 percent. So, I think even if we set our goals to 50
10 percent or 70 percent screening for memory complaints, it is
11 nice to do that but I don't think practically we are going
12 to reach that.

13 DR. KATZ: I will just reiterate what I said which
14 is that when you approve a drug you would like to at least
15 know that people could do it if they wanted to. We know
16 people don't read labeling very much but we still write it.

17 [Laughter]

18 So, there is a point to having formal diagnostic
19 criteria. At least it is, you know, what people should do.

20 DR. KAWAS: I would agree. When we looked at the
21 CDR concordance rate among experts, actually the whole room
22 did very, very well. Everybody agreed on the 3s. Everybody
23 agreed on the 2s. Almost everybody agreed on the 1s and the
24 0s. It was the 0.5s where we had the hardest time getting
25 people to agree. I think that the same can be said for

1 dementia and Alzheimer's disease. I mean, whether or not
2 you do a Mini-Mental, if a person walks in and can't tell
3 you their name you know they are demented. But MCI never
4 sticks its head out that way clinically. I think that it is
5 something that would take some probing and we would be
6 asking a lot of clinicians who don't fit things into their
7 repertoire so easily, which I think is why Dr. Temple's
8 suggestion was such an excellent one, to see if it could be
9 workable out in the community.

10 A couple more comments and then I am going back to
11 the FDA for some guidance.

12 DR. WOLINSKY: Is it necessary that we force our
13 population to have to see the lowest common denominator in
14 the community for their care?

15 DR. KAWAS: People in higher places than mine have
16 already made that decision, and I think we are not going to
17 go there at five o'clock. Now, Dr. Temple and Dr. Katz, I
18 realize that we absolutely danced around some of these
19 questions. Are there any that you would like us to dance
20 around a little more? I think you have heard a fair amount
21 of variety of opinions; a fair amount of conformity to those
22 opinions although they do kind of cover a spectrum of
23 semantics. I don't think we have really answered your
24 questions but I think you have heard a discussion on every
25 one of them.

