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FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
OPHTHALMIC DEVICES PANEL

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Salons A-C
Hilton Hotel Gaithersburg
620 Perry Parkway
Gaithersburg, Maryland

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IN ATTENDANCE:

Jayne S. Weiss, M.D., Chair

Arthur Bradley, Ph.D., Voting Member

Michael R. Grimmett, M.D., Voting Member

Alice Y. Matoba, M.D., Voting Member

Karen Bandeen-Roche, Ph.D., Consultant, deputized to vote

Stephen A. Burns, Ph.D., Consultant

Mark A. Bullimore, MCOptom, Ph.D.,
Consultant, deputized to vote

Andrew J. Huang, M.D., Consultant, deputized to vote

William D. Mathers, M.D., Consultant

Cynthia Owsley, Ph.D., Consultant, deputized to vote

William H. Swanson, Ph.D., Consultant, deputized to vote

Glenda V. Such, M.Ed., Consumer Representative

Ronald E. McCarley, Industry Representative

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1 P R O C E E D I N G S (8:30 a.m.)

2 DR. WEISS: I'd like to call this meeting of
3 the Ophthalmic Devices Panel to order, and we will have
4 introductory remarks from Sara Thornton.

5 MS. THORNTON: Good morning and welcome to the
6 104th meeting of the Ophthalmic Devices Panel. Before we
7 proceed with the agenda, I do have a few short
8 announcements to make.

9 I'd like to remind everyone who is new to the
10 sessions today to sign in on the attendance sheet in the
11 registration area. I'd actually like everyone to sign in,
12 but I know some of you have heard this announcement before.
13 But please do sign in right outside on the registration
14 table.

15 All handouts for the meeting are available out
16 there on the table, and we'd like, if you have messages for
17 the panel members, the FDA participants, if you need
18 information or have special needs, they should be directed
19 to Ms. Annmarie Williams, who's over here by the door, and
20 Ms. Jennifer Weber. They're both available also at the
21 registration area.

22 The phone number for calls to the meeting area
23 is (301) 977-8900, and in consideration of the panel, the
24 sponsor, and the agency, we ask that those of you with cell
25 phones and pagers please turn them off and put them on

1 vibration mode while you're in this room.

2 Lastly, will all meeting participants please
3 into the microphone, directly into the microphone, less
4 than four inches away, according to my instructions, and
5 give your name clearly, so that the transcriber will have
6 an accurate recording of your comments and others will be
7 able to hear you.

8 Now, at this time, I would like to announce to
9 those new to the session today the confirmation of the new
10 Ophthalmic Devices Panel Chair, Dr. Jayne Weiss, to my
11 left. We also have three newly appointed voting members,
12 Dr. Anne Coleman, Allen Ho, and Timothy McMahon, who are
13 regrettably unable to be with us today. However, we look
14 forward to their attendance at future meetings.

15 I'd also like to extend a special welcome and
16 introduce to the public, the panel, and the FDA staff three
17 panel consultants who today are with us for the first time.
18 Dr. Stephen Burns, on my left, who comes to us from Boston,
19 Massachusetts, where he is a senior scientist at the
20 Schepens Eye Research Institute and an associate professor
21 at Harvard University. Dr. Cynthia Owsley, to my right, is
22 from Birmingham, Alabama, where she is a professor of
23 ophthalmology in the School of Medicine and co-director of
24 the Center for Research on Applied Gerontology at the
25 University of Alabama. Lastly, Dr. William Swanson, on my

1 right, is a senior research scientist in the Department of
2 Clinical Sciences at the State University of New York
3 College of Optometry in New York, New York.

4 I'd like now to read the conflict of interest
5 statement for this session of the 104th meeting. "The
6 following announcement addresses conflict of interest
7 issues associated with this meeting and is made part of the
8 record to preclude even the appearance of an impropriety.

9 "To determine if any conflict existed, the
10 agency reviewed the submitted agenda for this meeting and
11 all financial interests reported by the committee
12 participants. The conflict of interest statutes prohibit
13 special government employees from participating in matters
14 that could affect their or their employers' financial
15 interests. However, the agency has determined that
16 participation of certain members and consultants, the need
17 for whose services outweighs the potential conflict of
18 interest involved, is in the best interests of the
19 government.

20 "Therefore, waivers have been granted to Drs.
21 Mark Bullimore and Stephen Burns for their interests in
22 firms that could potentially be affected by the panel's
23 recommendations. The waivers allow these individuals to
24 participate fully in today's deliberations. Copies of
25 these waivers may be obtained from the agency's Freedom of

1 Information Office, Room 12A-15 of the Parklawn Building.

2 "We would like to note for the record that the
3 agency took into consideration other matters regarding Drs.
4 Arthur Bradley, Michael Grimmett, and Jayne Weiss, who
5 reported interests in firms at issue, but in matters not
6 related to today's agenda. The agency has determined,
7 therefore, that they may participate fully in all
8 discussions.

9 "Lastly, we would like to note for the record
10 that Drs. Henry Edelhauser, Bernard McCarey, and Liliana
11 Werner, all invited guest speakers today, reported
12 interests with firms at issue. Dr. Edelhauser reported a
13 personal financial interest, a consulting relationship, and
14 a professional relationship in the form of contracts and
15 research grants. Drs. McCarey and Werner reported
16 professional relationships in the form of contracts,
17 grants, or research.

18 "In the event that the discussions involve any
19 other products or firms not already on the agenda for which
20 an FDA participant has a financial interest, the
21 participant should excuse him or herself from such
22 involvement and the exclusion will be noted for the record.

23 "With respect to all participants, we ask in
24 the interest of fairness that all persons making statements
25 or presentations disclose any current or previous financial

1 involvement with any firm whose products they may wish to
2 comment upon."

3 Thank you, Dr. Weiss.

4 DR. WEISS: Thank you, Sally.

5 We're going to have some comments at this point
6 by Mr. David Whipple.

7 MR. WHIPPLE: Thank you.

8 I only had one comment that I wanted to make
9 this morning. I wanted to thank this panel for yesterday's
10 discussion of the labeling for the wavefront technology
11 LASIK device. I know it was long and difficult, but a very
12 important discussion for us in the agency. Not only will
13 we use your comments and recommendations as guidance in a
14 framework for building labeling for devices of this type,
15 but we will also use it for monitoring the promotion and
16 advertising when they go to market their products as well.
17 So thank you for that discussion yesterday.

18 DR. WEISS: Thank you very much.

19 We're going to proceed to the open committee
20 session and start with the FDA presentation. Excuse me.
21 I'm out of order. We're going to start with the open
22 public hearing session and Dr. John Vukich of the
23 University of Wisconsin is going to make his presentation.

24 DR. VUKICH: Thank you and good morning.

25 DR. WEISS: Would you be able to start by --

1 just start by identifying yourself and your conflicts, if
2 any. Thank you.

3 DR. VUKICH: Okay. Thank you.

4 My name is John Vukich. I am an associate
5 professor at the University of Wisconsin in the Department
6 of Ophthalmology. I'm an investigator and medical monitor
7 for Staar Surgical, and it is from this experience that I
8 draw the information from which I form my opinions that I
9 will be presenting this morning.

10 My testimony today, however, is as an private
11 citizen. I have not received support or reimbursement for
12 my visit today, but I'm here to speak on behalf of phakic
13 IOLs as a segment of the refractive industry and as an
14 option for the correction of myopia.

15 Right now, LASIK is gold standard by which we
16 need to compare all future refractive technologies. We're
17 clearly trying to improve the outcomes of LASIK, and I
18 believe the decision yesterday to allow custom ablations is
19 a step in that direction. Any new technology that comes
20 along certainly is going to be compared to LASIK, and what
21 I'd like to do is present some information on the
22 comparison of LASIK and phakic IOLs.

23 We have looked at this in my practice. I am
24 primarily a refractive surgeon. Most of my practice revolves
25 around this. We looked at 198 phakic IOLs with a mean

1 myopia of -10. We compared this to a similar number, 219
2 LASIK patients similarly high myopia of between -9.5 to 12.
3 The mean was -9.5. Predominately female and younger
4 patients in their mid-30s.

5 When we looked at the percent of patients who
6 achieved 20/20 or greater, again, in this relatively highly
7 myopic group of patients, we found that about 32 percent of
8 patients on their treatment achieved 20/20 or better with
9 LASIK -- again, with a mean correction of close to -10 --
10 and close to 50, or 48.5 percent, were able to achieve
11 20/20 or better with phakic IOLs, and this was
12 statistically significant. The curve did fall off towards
13 the end and this was due to an early in the clinical trial
14 difference in the nomograms, and this curve has in fact
15 stayed the same all the way out and has remained consistent
16 for this difference.

17 So we believe that phakic IOLs, at least as a
18 single procedure, offer an alternative to LASIK in the
19 quality of vision that a patient might expect in the higher
20 ranges.

21 We know that recovery of visual acuity is an
22 important issue. Ultimately, patients need to retain their
23 visual acuity, but the rapidity of recovery is also an
24 issue, and the length of disability is an important issue,
25 of course.

1 When we look at lines lost or gained early in
2 the recovery at one week, we see that with LASIK, again in
3 the higher ranges, it is not uncommon -- almost 28 percent
4 of patients lost two lines or more of acuity early on, and
5 we can explain this because of epithelial irregularities,
6 surface irregularities, or edema in the early postoperative
7 period. We contrast that with phakic IOLs, in which not a
8 single patient in this clinical trial lost two lines or
9 more of visual acuity at week.

10 When we look at six months out, of course, we
11 would expect the epithelial changes to have recovered, and
12 in fact that is the case. However, there still were 6
13 percent of LASIK patients who had lost two lines or more.
14 This predominately fell from 20/15 to 20/25. Nevertheless,
15 this is a demonstrable loss of quality of vision that has
16 persisted through six months. Again, contrasting with
17 phakic IOLs, in which there was not a single patient who
18 had lost two lines of visual acuity. So in terms of
19 preservation of acuity, we believe that phakic IOLs offer a
20 good alternative, and perhaps superior, to corneal ablative
21 procedures.

22 We have anecdotal reports that patients prefer
23 the quality of vision with phakic IOLs. There have been a
24 limited number of patients who have had a phakic IOL in one
25 eye and LASIK in the other, and we have heard in fact that

1 at least one clinical trial from a prominent researcher in
2 Greece was discontinued because of the strong preference of
3 the phakic IOL eye and it was felt that continuing on that
4 did not make sense for them.

5 So based on this, we felt that perhaps maybe
6 there was something we could do to demonstrate a
7 difference, and what we have done is we have looked at
8 wavefront analysis as an objective assessment of optical
9 quality, and have now looked at comparison of the induced
10 aberrations in patients who have either received a phakic
11 IOL or LASIK.

12 These were 10 patients, 20 eyes, two eyes in
13 each patient. The mean myopia in the phakic IOL group
14 was -12 ranging to -15. The LASIK group ranged up to -10.5
15 with a mean myopia of 8.75 or a few diopters less.

16 When we looked at coma group means square
17 values, for phakic IOLs the average value was .22 or less
18 than half of the amount of coma observed in LASIK patients
19 postoperatively, and this was highly significant at the
20 .001 level.

21 We can do image convolutions to demonstrate
22 this difference looking at the standard Snellen chart.
23 This is what a patient might expect to see in simulation
24 with this much induced coma in LASIK, and this is what they
25 might expect to see with this much induced coma from a

1 phakic IOL.

2 We can do the same image convolution with a
3 photograph. Again, with LASIK and with the phakic IOL, and
4 we believe that there's a demonstrable difference in the
5 quality of the images that the patients see and what we can
6 demonstrate mathematically.

7 We looked at spherical aberration as well as an
8 isolated fourth-order higher term, and we see that there
9 were three times as much induced, or at least three times
10 as much observed, RMS of spherical aberration in the LASIK
11 compared to the phakic IOL. Again, significant at the .001
12 level.

13 When we look at the image convolutions of this,
14 we see the LASIK image compared to the phakic IOL image,
15 and again we can look at photographic convolutions with
16 LASIK and with the phakic IOL.

17 All of these images again demonstrate what we
18 have heard anecdotally, and that is that the patients with
19 phakic IOLs seem to be very pleased with the quality of the
20 image that they receive.

21 These images or these RMS values do combine and
22 it would probably make more sense to look at the
23 combination of terms. When we look at spherical and coma
24 RMS combined, we see LASIK versus phakic IOL, and once
25 again the image with phakic IOL.

1 Well, custom corneal ablation is not ideal
2 option for high myopia. The approval up to -7 yesterday I
3 believe is a step forward in our ability to correct myopia,
4 but one of the issues that I think will limit this
5 application is the fact that it can remove up to 20 microns
6 of tissue per diopter with larger ablation zones and with a
7 custom application. I believe this will ultimately limit
8 custom ablations to ranges that are already approved, at
9 least from one manufacturer, but in fact the simple physics
10 and the simple anatomy may eliminate this as a possibility
11 for higher corrections. So it would certainly be
12 beneficial to have a noncorneal alternative.

13 There is in fact a limit to how much corneal
14 tissue can be removed. This is a macroscopic view of a
15 cadaver eye that has had corneal tissue removed down to a
16 level of 100 microns. This is clearly thinner than what we
17 would do clinically, but it does demonstrate grossly the
18 elastic character of the posterior surface of the cornea
19 and again is consistent with what we can observe with
20 advanced imaging technologies.

21 Corneal ablation is certainly not appropriate
22 for some patients no matter what the correction achieved.
23 Patients with keratoconus, as demonstrated here, clearly
24 would not be suitable for corneal reshaping, but there are
25 certainly many more patients who have subtle changes that

1 come to our attention when we screen them for refractive
2 surgery, changes of mild elevation, changes on the
3 posterior surface elevation, or keratometric changes that
4 are subtle variants of what we would consider an abnormal
5 corneal topography or corneal anatomy, and in fact a
6 noncorneal alternative may be a superior alternative for
7 these patients as well.

8 The fact remains that there are few options
9 available to patients who have high myopia. This has led
10 to some options being employed that are not approved and in
11 fact may pose dangerous situations for patients. We have
12 certainly seen clear lens extraction as an unapproved use
13 of an approved IOL for cataract surgery, but again used in
14 a refractive manner. This is controversial. However, it
15 is being done.

16 With one anecdotal report from a clinical trial
17 center in the United States of a refractive-based practice,
18 we looked at the incidence of clear lens extraction before,
19 during, and after the availability of phakic IOLs in this
20 individual practice. The white bar beneath represents the
21 time during which enrollment was available for phakic IOLs,
22 and we can see that there was a significant decrease in the
23 total number of clear lens extractions performed as a
24 refractive procedure. At the conclusion of enrollment,
25 there was an over doubling of the number of clear lens

1 extractions.

2 Again, this is consistent with the researcher's
3 or with the investigator's observation that given an
4 alternative, this particular researcher would shy away from
5 clear lens extractions, and we believe that this is a
6 better alternative and perhaps something that I think would
7 offer our patients perhaps a better, or we hope safer,
8 alternative.

9 In conclusion, I would like to suggest that
10 corneal refractive surgery is an excellent opportunity for
11 patients. Many of them enjoy -- most all enjoy -- the
12 benefits of this, but I believe that a noncorneal
13 alternative is an important step forward. I believe that
14 the safety and efficacy of phakic IOLs needs to be
15 demonstrated, but certainly the opportunity to provide
16 quality of vision seems to be quite high.

17 DR. WEISS: Thank you.

18 Do any of the members of the panel have any
19 questions for Dr. Vukich? I would actually start off with
20 one question myself, which is how would you weigh the
21 potential risks of intraocular surgery -- namely,
22 endophthalmitis, albeit rare, and corneal edema -- against
23 the benefits of the visual recovery and quality of vision?

24 DR. VUKICH: Well, certainly, any time we go
25 inside the eye, we have to hold a different standard than

1 we would on the surface. We know that infection is an
2 option, or at least is a problem, with LASIK, albeit rare,
3 but it's somewhat devastating when it does occur. It is
4 something that needs to be looked at very carefully in
5 terms of the real incidence.

6 I think the bigger issue in my opinion is the
7 potential for removability of these devices, and that is
8 that there is an alternative to restore the eye perhaps not
9 exactly to what it was preoperatively, but to remove
10 whatever the patient may not have liked about the quality
11 of vision. If there is edge glare or halos or night vision
12 problems or decentrations with LASIK, the remedies are
13 typically not satisfactory, and in fact with the phakic
14 IOL, at least the opportunity to reverse that or remove the
15 offending treatment certainly I believe offers a
16 significant advantage.

17 DR. WEISS: Depending on if the offense is
18 irreversible endothelial cell loss or infectious organisms
19 or cataract formation.

20 DR. VUKICH: Very clearly, those are things
21 that have to be looked at. Endothelial cell counts are a
22 critical issue, as are the potential for infection.

23 DR. WEISS: I think Dr. Bradley had a question,
24 and Dr. Bullimore as well. Let's start with Dr. Bradley.
25 Dr. Bradley, Dr. Bullimore, and then Dr. Mathers.

1 DR. BRADLEY: I was just looking at your slide
2 where you showed visual acuity as a function of time after
3 the procedure, and I didn't quite follow your explanation
4 of why the phakic IOL percent of patients achieving 20/20
5 fell off at 12 months. You sort of ran through some sort
6 of excuse it sounded like.

7 DR. VUKICH: I'd like to think of it as the
8 reason. The early nomograms for calculation of power will
9 be represented at the last data point collected as time
10 goes on. So the first several phakic IOLs that were
11 implanted in this clinical trial systematically
12 undercorrected all the patients, and mid-course adjustment
13 or early-course adjustment and the attempted correction
14 versus achieved correction became substantially better. So
15 that dip between six months and 12 months, which was the
16 two data points at six months and 12 months and there was
17 no in-between visit, remains something that between 12
18 months and two years we have seen that seem dip, and now
19 between two years and three years we see that same dip. It
20 is just simply the leading edge representing the earliest
21 patients who were enrolled, but the remainder of the line
22 stays as it has been with the improved nomogram.

23 DR. BRADLEY: Thank you.

24 DR. WEISS: Dr. Bullimore?

25 DR. BULLIMORE: Yes, this is Mark Bullimore.

1 If my memory serves me correct, one of the issues discussed
2 by the panel at previous visits to this phakic IOL guidance
3 document was whether these devices should be held to the
4 same standard as LASIK. What's your impression?

5 DR. VUKICH: To the same standard in what
6 regard?

7 DR. BULLIMORE: In terms of, say, vision.

8 DR. VUKICH: In terms of quality of vision?

9 DR. BULLIMORE: Yes.

10 DR. VUKICH: I believe that that is both
11 appropriate -- I don't know that we would want to see a
12 step backward in the evolution of any technology, and so
13 holding to the same standard I believe makes sense.

14 DR. BULLIMORE: So in the absence of any other
15 information, you would argue that we should use the same
16 criteria for uncorrected visual acuity and corrected visual
17 acuity and loss of visual acuity that is currently used for
18 refractive lasers?

19 DR. VUKICH: I think that makes sense. I think
20 that it would also make sense to stratify the data into the
21 various ranges of power that you're looking at, knowing
22 that the standard for LASIK at -12 diopters should be
23 different than the standard at -1 or -2, and that the
24 outcome at that level could be a different expectation.

25 DR. BULLIMORE: You mean in terms of safety or

1 efficacy or both?

2 DR. VUKICH: Both.

3 DR. BULLIMORE: So you would expect your LASIK
4 patients in your -10 group to be not doing as well as
5 patients with lower degrees of myopia?

6 DR. VUKICH: I would expect higher enhancement
7 rates. I would expect potentially higher levels of
8 reported edge effect, glare, and those sort of symptoms in
9 the higher ranges. We might also anticipate that the
10 higher ranges of LASIK may in fact become lower as we
11 implement custom corneal ablations limited by the tissue
12 effect that needs to be removed. We simply don't do -12
13 LASIKs anymore. At least, I don't, and many reputable
14 surgeons or high-volume surgeons have lowered the upper
15 limit at which they will perform LASIK, and that number I
16 believe is still going down.

17 DR. BULLIMORE: But clearly there are some less
18 than reputable people doing a lot of clear lens exchange.

19 DR. VUKICH: Again, I can't speak to the
20 decisions that other surgeons make.

21 DR. BULLIMORE: Okay. That's fine.

22 DR. VUKICH: In the face of not having an
23 alternative, it seems to be happening.

24 DR. BULLIMORE: Yes. And one final question.
25 I mean, you presented data on 200 patients who had phakic

1 IOLs and LASIK. Were they all from your practice?

2 DR. VUKICH: Yes.

3 DR. BULLIMORE: And where these people who had
4 the phakic IOLs, were they single device?

5 DR. VUKICH: Excuse me. The phakic IOLs were
6 part of the multicenter trial. Excuse me. All the LASIK
7 patients were from my practice.

8 DR. BULLIMORE: Okay. Thanks very much.

9 DR. WEISS: Dr. Mathers?

10 DR. MATHERS: Do you have any information about
11 observation of cataract formation that might have occurred
12 later? I mean, these lenses have been implanted for some
13 time now, but we don't see any data on three years, four
14 years, or whatever, and certainly something was implanted a
15 little bit longer than we have seen data for.

16 DR. VUKICH: Yes, and we are collecting data
17 and do have a substantial amount. In fact, all of the
18 patients in at least one of the clinical trials is
19 submitted. Not submitted, but is through the two-year
20 point, and we're about halfway through the three-year
21 collection of data. So yes, that data does exist on the
22 formation of cataracts in all of the safety and efficacy
23 parameters that were approved in the protocol that's been
24 undertaken. Again, I am not prepared to do a thorough
25 disclosure or presentation of that information, other than

1 to say it is going to be submitted and we believe
2 represents a standard that we believe is acceptable.

3 DR. WEISS: Dr. Huang?

4 DR. HUANG: Given the known potential
5 complications of cataract, glaucoma, and retinal
6 detachment, are you implying that this phakic IOL device
7 should be limited to the higher myopias?

8 DR. VUKICH: Ultimately, the complication rate
9 is something that is going to determine whether or not
10 phakic IOLs will be appropriate. The quality of the optics
11 and the ability to correct a refractive error I believe is
12 intuitive and has been demonstrated and will be
13 demonstrated. Ultimately, how safe they are is going to be
14 the issue as to where they should be used.

15 If a product can be demonstrated to be safe at
16 any range, I see no reason that it should be limited only
17 to the higher myopic patients. I believe initially it
18 would make sense to offer this as an alternative for higher
19 myopic patients in which we know LASIK has limitations or
20 may not even be appropriate.

21 DR. WEISS: Dr. Grimmatt?

22 DR. GRIMMETT: Dr. Michael Grimmatt. Is your
23 experience with phakic IOLs mostly of the posterior chamber
24 type? You don't have any other experience or data
25 otherwise regarding anterior chamber, either angle-

1 supported or iris clip? Is that correct?

2 DR. VUKICH: All of my personal experience has
3 been with posterior chamber phakic IOLs.

4 DR. GRIMMETT: Okay. Thank you.

5 DR. WEISS: Just one follow-up question in
6 terms of the standards that the IOL should held to
7 visually. In a LASIK patient who has higher myopic error,
8 we can easily lift up the flap and enhance, but with a
9 phakic IOL, the risk of entering the eye again is higher
10 than a flap relift. With that in mind, would you still
11 hold them to the same visual results postoperatively?

12 DR. VUKICH: I think comparisons would need to
13 be made based on a one- or two-procedure comparison. I
14 believe that all of the trials for LASIK have been as a
15 single procedure without enhancement, and I think the
16 ability to enhance we understand is real and people can do
17 that, but I believe that all the submissions have been on
18 primary treatment, not enhanced data.

19 Now, the ability to do a minor -- or not minor.
20 To do a corneal treatment on top of a phakic IOL certainly
21 exists, although the answer to question is yes. Going back
22 in for a small refractive error probably could easily be
23 done on the corneal level, perhaps more appropriately so
24 than exchanging the implant.

25 DR. WEISS: Any other questions from the panel?

1 (No response.)

2 DR. WEISS: If not, thank you very much for
3 your presentation.

4 DR. VUKICH: Thank you.

5 DR. WEISS: Are there any other comments from
6 anyone else for the open public hearing session?

7 (No response.)

8 DR. WEISS: If not, we will now -- obviously, I
9 was anxious for the FDA presentation. So now, we will have
10 it.

11 MS. LOCHNER: I'm just going to make a few
12 introductory comments before we actually present the
13 questions to the panel.

14 Today we plan to discuss with the panel
15 clinical study design for phakic intraocular lenses. We
16 have prepared for your review a document entitled "Phakic
17 Intraocular Lenses: Clinical Guidance for Ophthalmic
18 Devices Panel Discussion, August 2, 2002," which is a
19 compilation of several activities in which the FDA
20 participates. It generally represents a composite of the
21 American National Standards Institute standard, the
22 International Organization for Standardization standard,
23 and the FDA's guidance document for phakic IOLs.

24 We last received the panel's recommendations
25 for phakic IOL studies in 1998 and so we thought it

1 important to receive updated recommendations from the
2 panel. We will then compile your recommendations and
3 present to the ANSI and ISO Standards Committees and update
4 FDA's guidance document accordingly. By having this
5 discussion today, we believe sponsors of these studies will
6 gain valuable information to successfully prepare
7 investigational device exemption and premarket approval
8 applications for their phakic IOLs.

9 We will begin this morning with presentations
10 from our invited speakers on two topics. First, Drs. Henry
11 Edelhauser and Bernard McCarey from Emory University will
12 discuss methodology and analysis for endothelial cell
13 density specular microscopy measurements. Next, Dr.
14 Liliana Werner from Storm Eye Institute will provide
15 background for the measurement and analysis of lens
16 opacity.

17 Following the invited speakers' presentation,
18 we will focus the panel's discussion on three areas.
19 First, the endothelial cell density study with Dr. Michael
20 Grimmett as the primary reviewer; second, measurement of
21 lens opacity with Dr. William Mathers as the primary
22 reviewer; and third, contrast sensitivity with Dr. Mark
23 Bullimore as the primary reviewer.

24 Questions have been provided to each of these
25 panel members for these topics to help to generate

1 discussion. However, we hope the panel will allow the
2 discussion to move to any area of significance to them. We
3 hope to step through each of the three areas -- endothelial
4 cell counts, lens opacity, and contrast sensitivity -- one
5 by one, opening each topic to full panel deliberations
6 after each of the primary reviewers' comments. After these
7 three primary areas have been discussed, Dr. Weiss will
8 open the discussion to comments on any section of the
9 clinical study guidance.

10 Unless there are any questions about the
11 agenda, I would like to move on to the invited speakers.
12 First, I'd like to express my gratitude to Drs. Henry
13 Edelhauser, Bernard McCarey, and Liliana Werner for taking
14 time from their schedules to present to us today. We are
15 honored to have people of their caliber providing their
16 insights to these important topics.

17 I would like to introduce the first two invited
18 speakers. Dr. Henry Edelhauser is professor of
19 ophthalmology and director of ophthalmic research at Emory
20 University University School of Medicine in Atlanta. He
21 received his Ph.D. from Michigan State University and
22 joined the faculty of the Medical College of Wisconsin. In
23 1989, he became the Ferst Professor of Ophthalmology and
24 director of ophthalmic research at Emory. He has served as
25 president of ARVO and has received the Honor and Senior

1 Achievement Award from the American Academy of
2 Ophthalmology. He also has received the Castroviejo Medal
3 and the Alcon Research Award. He presented a keynote
4 lecture at the 55th Congress of Clinical Ophthalmology in
5 Japan entitled "Cataract and Refractive Surgery: The
6 Effect on the Corneal Endothelium." His research interests
7 include surgical pharmacology, corneal physiology, drug
8 delivery, and ocular toxicology.

9 And Dr. Bernard McCarey is professor of
10 ophthalmology at Emory University School of Medicine and
11 affiliate scientist at Yerkes Regional Primate Center at
12 Emory. He received a Ph.D. from Marquette University and
13 joined the Department of Ophthalmology at the University of
14 Florida College of Medicine. He joined Emory in 1979 and
15 has served as chairman of their Institutional Animal Care
16 and Use Committee. He has received the American Academy of
17 Ophthalmology Section Honor Award, the Barraquer Award, the
18 Alcon Research Award, the CIBA Vision Research Excellence
19 Award, and Everett Kinsey Lecture Award at CLAO. His
20 research interests include corneal physiology, refractive
21 surgery procedures, ocular toxicology, and contact lenses.

22 And so, without further ado, I'll turn it over
23 to Drs. McCarey and Edelhauser.

24 DR. McCAREY: Thank you.

25 My name is Bernard McCarey. As you've been

1 told, I'm at Emory University. I have been interested in
2 specular microscopy as a laboratory science and also as a
3 clinical science. At present, I am a reading center for
4 Medennium.

5 What I'd like to discuss today with you is --
6 whoops. We're not moving forward. It's hooked up, but it
7 doesn't move.

8 DR. WEISS: I'd just mention at this point,
9 after all the speakers give their presentation, they can
10 actually sit at this table over here with your names there,
11 so the panel has an opportunity to ask you questions.

12 DR. MCCAREY: Now we're moving. Thank you.

13 There are several specular microscopy units on
14 the market presently and they break into two categories,
15 contact and non-contact. I present this as a list for your
16 handout. You can look at it later, but what I would really
17 like to do is to express to you the major differences
18 between the contact and non-contact.

19 Obviously, contact means you have to use an
20 anesthetic. You have to applanate the surface of the eye,
21 but you also are flattening the surface of the eye, and
22 when you do this, you generally can look at a larger field.
23 So generally, the contact units are considered large-field
24 specular microscopy. The non-contact has a smaller field.

25 You can see on the very bottom of your slide

1 we're talking about 700 or 800 cells can be visualized with
2 a contact unit, whereas only 160 or so for the non-contact,
3 and this has to do with the height of the slit. If we had
4 time, we'd go into specular glare, but basically the slit
5 in both of these instruments is the same width. It's just
6 a different height.

7 We are going to be collecting data about the
8 cell morphology, cell area, cell density, polymegathism,
9 which is an order of variation in size, and pleomorphism,
10 which tells you about how many sides there are on a cell.

11 I add this slide just for your notes. It
12 expresses the calculation for cell density and coefficient
13 of variation.

14 I also add this for groundwork. It gives you a
15 feeling as to what people would say at middle-age the
16 number of cells would be on a corneal endothelium, and it
17 varies with age. This is well-known in the literature and
18 we can find many references in the literature towards these
19 numbers.

20 But what I'd really like to show you is that
21 these numbers are from linear regression lines. They are
22 not a number. A person doesn't have a 2,700 cell density
23 because they're the age of 50. Rather, there's quite a
24 wide spread, as illustrated from this data from Dr.
25 Edelhauser in 1985. You can see a person of age 50 can

1 have anything from 2,200 on up to 3,300. So there is quite
2 a spread.

3 We also have a convention, an issue, that I'd
4 like to mention. That is, polymethism is often referred
5 to in the literature as a value like .27 for a normal young
6 adult, but you can also see 27. Don't be confused. It's
7 just a literature convention.

8 The spread in coefficient of variation is
9 sometimes even larger in the normal population, as
10 illustrated here. So please don't expect to find one
11 number.

12 The major question that we're going to have
13 here is if you do a surgical trauma or something else to
14 the eye, how representative is a central endothelial cell
15 density to the information of what happened to that tissue?
16 If you cause local damage in one area of the cornea, how
17 fast does it affect another area, what does that time
18 duration spell, and can you really look at central
19 endothelium and get a feeling for what trauma occurred?

20 I reached back in the literature back to '79,
21 and I use this not as an example of what a surgical
22 technique may do to the tissue, but rather as an example of
23 how the tissue responds to a surgical event.

24 In this case, there was phacoemulsification and
25 extracataract extraction, and what the person did was

1 they're obviously making an incision in the superior area,
2 going into the eye, potentially damaging endothelium in the
3 superior zone, and if we look at the control tissue, we can
4 inferior, central, and superior clustered together. After
5 the surgery, we see superior has dropped considerably,
6 central has less, and inferior less.

7 So the question is will this spread of damage
8 rapidly congeal to one point again? And if you look at
9 this data, for 24 months there was only slight difference,
10 and it took on up to five years or more before all three
11 zones expressed themselves with the same value. So these
12 things go slowly.

13 DR. BULLIMORE: Before we move on, am I correct
14 in assuming there's only three people in that last data
15 point?

16 DR. McCAREY: I'm glad you mention it. No.
17 There are three people, but what this data did was he
18 collected the data at one time point. So he had 28
19 patients and some of them were out five years and some were
20 out four years or whatever, and he just collected the data
21 in that manner. Yes, there are very few data points in
22 each one of these, but I show this as an illustration as to
23 what can occur.

24 As another example, we're looking at data from
25 intracapsular cataract extraction, and if I point just to

1 mean cell area, you look at rapid changes going on for the
2 first four months and then some kind of a linear response.
3 Now, this is characteristic, if we looked at keratoplasty,
4 where you'll see much the same kind of event, rapid changes
5 -- in this case, six months -- and then a progressive
6 change. So this gives you a feeling as to when you might
7 want to collect data because of the kind of tissue
8 response.

9 If we reach back into the literature from Dr.
10 Bourne, we can see that he chose to follow patients for 10
11 years after cataract extraction. It doesn't matter if it's
12 with or without an implant. The point is that he followed
13 the patients for 10 years and he saw a rather in form cell
14 loss of 2.5 percent per year.

15 We often are referring to what a normal patient
16 would lose as far as endothelial cell density over time
17 simply because of aging, and we can refer to a paper by
18 Bourne. He says he followed them up for 10 years and he
19 has .6 percent, plus or minus 5 percent. I feel that's a
20 rather conservative number, but this is a number that's in
21 the literature.

22 One of the things we must realize is that we're
23 often using patients in clinical trials, such as refractive
24 surgery clinical trials, and these patients have a history,
25 and the history may often be contact lenses. So we're

1 entering patients in that are not "pure normal" patients,
2 but somebody that has a history of some kind of possible
3 trauma to the endothelium, and we can definitely say in the
4 literature that there are both transient problems with
5 contact lens wear, but also chronic problems in which we
6 have pleomorphism and polymegathism shifts in the tissue
7 over time.

8 So these patients will often look like this,
9 and I point these three examples out because you'll notice
10 that the cell densities are all fairly high and all fairly
11 much the same. Cell density is not going to give you the
12 full answer as to what that history of the patient was. We
13 have to look at the coefficient of variations, and we'll
14 see that they vary from 45 on up to 76. They can be quite
15 high, and that's expressing the fact that we have some
16 large cells interdispersed among the smaller cells.

17 The way we're going to analyze this tissue is
18 by multiple methods out there in the literature. The first
19 one is a comparison method. Look at a picture, look at a
20 honey comb, and how many cells do we have? It just tells
21 you cell density.

22 The frame method is another method. Just cell
23 density.

24 The next two methods, corner method and center
25 method, are going to give you actual cell area, and from

1 that we can calculate coefficient of variation and other
2 values.

3 Let's take a moment to look at the frame
4 method. The technique is, on the screen or from a
5 photograph, you put a box, and then you simply count the
6 cells within the box. The box is a small portion of a
7 millimeter. You adjust it up to a full millimeter, and
8 that's going to be the answer. So you just simply get cell
9 density.

10 One of the really easy pitfalls in this is that
11 in this example I've made a blue box, and the data over
12 here is in blue, and a yellow box. The blue box is twice
13 the surface area of the yellow box, even though it may not
14 look it, and if you give somebody an opportunity and tell
15 them to put a box on a field, they're going to make a small
16 box. What this means is that if it's twice the surface
17 area, if you counted 90 cells within the blue box, you have
18 to multiply it by 27 in order to get it up to a full square
19 millimeter. If you had the yellow box, you'd count 45 --
20 it was half the size -- and you'd have to multiply it by
21 55. So right off the bat, you have a two-fold error
22 magnifier in your calculations simply by the size of the
23 box, and most people make small boxes.

24 The other method is the center method. In this
25 one, we put dots in the center and calculate what the

1 nearest neighbor is, and from this you calculate a polygon,
2 which is the cell, and so forth. Dr. Edelhauser will
3 discuss the patterns of this method in a few moments.

4 One of the things we must worry about is if you
5 put the dot offcenter, does it louse up the calculation?
6 And with the Konan software, you have a very nice
7 opportunity of simply a dot and then asking for this
8 analysis. Come back, move another dot, ask for the
9 analysis.

10 So I did this for 10 different cells, and you
11 can see that the error is fairly small. It's less than 1
12 percent.

13 I then dropped a cell. That is, took a dot
14 away, and tried it with various sizes of cells, and it
15 didn't seem to matter. I even used a hexagon pattern,
16 which was a perfectly uniform pattern, and it looked like
17 each cell that you missed the dot on, you lost about a
18 percent in the accuracy of the answer.

19 Another question is how many cells do we need
20 to count? This is the classic one you see in the
21 literature. If you count more cells, you get a more
22 accurate answer.

23 So I got a large field like this, divided it up
24 into multiple boxes, and then counted 10 cells, 20 cells,
25 30 cells, and so forth to create a series of lines, as

1 illustrated on this. So each one of these is an effort of
2 increasing the number of cells in the count.

3 You'll notice if you have a uniform, low
4 coefficient of variation cell pattern, you can get a fairly
5 good answer right off the bat. It improves when you get to
6 about 50 and it's a slight improvement beyond that. So you
7 don't need to count an awful lot of cells.

8 Coefficient of variation? It's a little bit
9 noisier. You certainly want to be over 50 cells counted in
10 order to get a reasonably uniform answer, but there's
11 always a spread in the answer.

12 This is more real life. This is a patient that
13 may have had a contact lens or some history of something or
14 simply an older patient with a higher coefficient of
15 variation, 45. Do the same kind of analysis. Now look at
16 the spread. It's tremendous. If you counted 25 cells, you
17 could have anything from 2,000 to 3,200 for cell density.
18 It gets better over 50 or 100 cells, but it never gets
19 really tight.

20 Coefficient of variation is even worse. This
21 is just summarizing. You can look at this on your handout,
22 but basically it says that if you have a large coefficient
23 of variation, you're going to get a larger spread and you
24 can't get away from that.

25 Also I want to mention some of things that are

1 pitfalls in the analysis. That is, when you ask the
2 clinical site to count 100 cells, they may tap 100 cells on
3 the cell pattern, as illustrated here on your right, but
4 the analysis using nearest neighbor -- for instance, if
5 this was seven dots and you asked for the calculation to be
6 performed, you'd only see that you actually counted one
7 cell, the one in the center. The others were just nearest
8 neighbor in the analysis.

9 So if you want somebody to count 100 cells,
10 coming down we have to count actually about 140 cells in
11 the analysis. Now, that sounds like a small point, but
12 when you have a limited field to look at, you may not be
13 able to achieve that because there simply aren't enough
14 cells on the field.

15 This shows data from a Medennium clinical
16 trial. These are strictly the control eyes, 123 good
17 images plotted out after the counting, and we had
18 everything from 900 or so on up to 3,600.

19 You'll notice that if you had asked for 100
20 cells in the analysis, we'd have to have a field of about
21 2,400 cell density. Less than 2,400 cell density, there
22 simply aren't the cells to look at in the specular
23 microscope field if using the Konan specular microscope.

24 Then every once in awhile we'll get poor
25 images, which we are unfortunately forced to use because

1 maybe the control data wasn't better than that, and you're
2 really using very few cells in the analysis.

3 Another issue is how uniform is the surface of
4 the eye. This happens to be my eye, and what I did was I
5 looked at the central target, I looked at a little bit
6 further out -- 1 millimeter, 2 millimeters, and 4
7 millimeter zones -- and then I took pictures as I looked in
8 various spots on the field, as you can see here.

9 Then I asked the question, statistically, is
10 this dot the same as this dot and so forth? And it came
11 out to no. So my surface, even though I have no history of
12 contact lenses and so forth, has a lot of variability, and
13 if you took answers from all over the place, you are going
14 to look like multiple patients. It's not going to look
15 like one patient.

16 Narrow the field down, still the same problem.
17 Narrow it down, still the same problem. Get down to about
18 a millimeter out and it's certainly better, but it's really
19 good if you look at the dead center. If I looked at that
20 green target very carefully and took 10 pictures in a row,
21 they would really look like the exact same patient.

22 There is a little trick involved in this, and
23 that is I happen to be an emmetrope -- these are reading
24 glasses -- so as I look off at the target inside the
25 machine, I see what you see on that screen, a red circle

1 with a green dot. If a person is a myope with 2 or 3
2 diopters off, he sees a blur, and so asking him to
3 cooperate to look at dead center becomes an increasing
4 challenge.

5 One more piece of data. What I did was I
6 looked at the control data from the Medennium group that I
7 have and there's a single reading group, which is me, but
8 there are 58 subjects at seven clinical sites. So this is
9 real life. The patients had a real-life coefficient of
10 variation, 36, not the nice normal of 25 or so, and what we
11 did was we had data collected at baseline and three months,
12 and I asked the question on that patient is the baseline
13 the same as the three-month data? And what it showed me in
14 a paired T-test was a .7, which is pretty good.

15 But there's a little more to the story. If I
16 then looked at the data and massaged it a little bit
17 further and graphed out the percent difference between
18 these two time periods for each of the patients and then
19 made a cumulative graph on your Y axis, I can then ask if I
20 have a spread of 2.5 percent, how many patients are going
21 to fall in that group? And this said 50 percent. So you'd
22 have to have less than 2.5 percent difference between these
23 two numbers to have 50 percent of your patients in your
24 group. If we wanted all of the patients, we'd have to go
25 up to 9 percent to get 100 percent.

1 So it's really quite surprising, and there are
2 references in the literature that support these kinds of
3 numbers. We're not looking at 1 or 2 percent spread in the
4 data between these two time periods. In this group, we
5 were looking at 9 percent. So we'd have to have a 10
6 percent change in the event in order to be 100 percent sure
7 that it was caused by the event, rather than just the
8 spread.

9 Some guidance for setting up clinical trials.
10 You certainly want to have careful control of the criteria
11 of your study, which specular microscope you're using, your
12 experience, and the data capture. Who's doing the capture
13 and how often does he do it and how much experience? How
14 many sites are located? Each time you add a site, you're
15 increasing the variabilities.

16 So let's go right down to the final slide and
17 what I would suggest. First of all, I would suggest we all
18 have the same microscope, and I like the non-contact
19 specular microscope simply because it means you're asking
20 for less skill from the technician.

21 I prefer one technician, I prefer to train that
22 technician, and I'd like to check on the training of that
23 technician to see if they really are doing it frequently
24 enough that they have kept their skills up. Most of these
25 people have lots of other things to do and they kind of get

1 soft on their skills.

2 I think a central reading center to limit some
3 variability is also a very good idea.

4 Thank you very much.

5 DR. WEISS: Thank you very much. You can take
6 a seat when you're done, Dr. McCarey, at the table.

7 DR. McCAREY: I'm rebooting for the next one.

8 DR. WEISS: Oh, you're rebooting.

9 DR. EDELHAUSER: While Dr. McCarey's doing
10 that, I'm Dr. Henry Edelhauser, and I'm at Emory. My
11 laboratory has been a reading center for KeraVision and
12 Staar, and I do a number of research contracts with Alcon
13 on intraocular irrigating solutions.

14 What I'd like to summarize for everybody today
15 is a very practical summary now of what Bernie talked about
16 and a little bit of the theory, and Dr. Ramzy Azar was the
17 one that helped out and was one of our major reading center
18 individuals, though he's presently in the Navy right now
19 down in Bethesda.

20 The purpose of what I'd like to summarize today
21 is using the robo non-con specular microscope, which seems
22 to be about the best specular microscope to run a clinical
23 trial, and particularly when you're thinking about
24 refractive surgery, because you're not applanating onto the
25 cornea. So we want to understand the variable issues that

1 may be found in specular microscopes. So our objectives in
2 this 10-minute presentation are to provide good examples in
3 good and poor photography, illustrate the variability, and
4 illustrate the variability within a single image that data
5 has to be obtained from.

6 What is a good image? I think Dr. McCarey
7 showed you. This is typical panel that one would receive
8 from the robo non-con. You notice on here you can find
9 distinct cells. You can identify at least 150 cells. The
10 cells can be grouped in a very uniform manner.

11 Then you may have to say, well, what may be
12 good for clinical purposes may not be good for research.
13 For example, in many clinical times, they'll only count 15,
14 20 cells, but for a research study, particularly where
15 you're quantitating endothelial cells over a long time, you
16 want to try and put a dot in every one of these corneal
17 endothelial cells.

18 Things to consider that may affect the optical
19 image. Dry eye, contact lens use, wrong specular
20 microscope settings -- you can go into the manual mode with
21 the non-contact -- and patients with keratoconus are very
22 difficult to get endothelial specularscopes.

23 Patient compliance. This is a real issue if
24 the individuals can't see that little green circulating dot
25 and you have to work with the patient. So training becomes

1 very important.

2 Age of the patient, a little bit more
3 difficult, and then training and experienced photographer,
4 and as I emphasize over and over again for individuals and
5 companies that are trying to under specular microscopy, you
6 have to train the individual out in the field.

7 Poor quality images are something that are an
8 issue, and particularly with preoperative because if your
9 preoperative photos are poor quality, this is going to
10 carry through the whole study.

11 Here is an example where you have just a panel
12 over here, and here's another panel here. So really what
13 was happening is that the patient was moving his eye when
14 this picture was captured.

15 Another type of poor quality image. Very
16 difficult. Here you might be able to obtain 30 to 40 cells
17 in this particular panel. If this was a preop, this
18 patient is lost because there's identifiable cells that
19 could be measured.

20 Again, poor quality images where it's very,
21 very difficult, and I can tell you from being involved in a
22 reading center and looking at over 10,000 of these with the
23 laboratory, you get photos like this that are preoperative
24 and when you want this as a preoperative photo, how do you
25 start a baseline for this particular individual? This is

1 where training of the photographer or the individual
2 running the specular microscope out in the field is very
3 important because that image will come up on the screen,
4 and if it's this one, they should sit the patient down
5 again and retake the photograph.

6 Conditions that potentially increase
7 variability. Patients that have Fuch's, polymegethism,
8 pleomorphism, injury, and low cell density. Particularly,
9 there are some patients that do have a low cell density.

10 Here's an example of a patient that has guttata
11 or Fuch's, and notice you see these black spots here.
12 Actually, these black spots are covered by a very, very
13 thin part of the corneal endothelial cell and the
14 refractive index is different here. Well, how do you
15 analyze this photograph? Well, you'd have to group here or
16 you'd have to group here.

17 So capturing the best image is very important.
18 You have to make sure the patient is comfortable. You have
19 to instruct the patient to blink. You have to instruct the
20 patient not to move and to open his eyes wide. You have to
21 instruct the patient to focus on the green light, and as
22 Dr. McCarey said, it's difficult for somebody who has type
23 of disease or is extremely myopic because you can't see the
24 green light as well as somebody who's an emmetrope. You
25 have to be patient. You have to work with that patient and

1 use of the manual setting to improve the quality of the
2 cornea is -- sometimes the corneas are thicker than the
3 normal setting, so you have to go to the manual.

4 Things to consider when you analyze images.
5 You have to locate the best and most representative area,
6 the number of cells, you have to look at the quality of
7 cells, and you have to use the area with the fewest
8 distortions, as I'd shown in the very early aspect.

9 Here is an example of the best image. Well,
10 the best image on this specular here would have to be here,
11 and this one you'd have a very hard time finding the best
12 image. It may be somewhere along in this area.

13 Dotting cells. You have to dot all the cells
14 in the center and you have to remain accurate and
15 consistent throughout. We always recommend dotting at
16 least 150 cells if there are 150 or more than that on the
17 photograph because at least you'll get an analysis of 100
18 cells, 110 cells, and as Dr. McCarey showed you on the
19 graph, the more cells you can dot, the better the
20 statistical analysis will be.

21 Where to group the analysis? Now, this is
22 interesting. Well, if you could dot every one of these,
23 this would be the appropriate way to go, but if you dot
24 here, if you would look here, you'd have a lot of big cells
25 up in this area and small cells here. So certainly, the

1 diversity in the cell count would be very large, and this
2 is one of the disadvantages of having specular microscopy
3 done out in the field and have the technician because the
4 technician may just pick this area and then that will be
5 the preop, or they may pick this area, and then you come
6 back and your three-month data or six-month, they're going
7 to analyze up here in this area. So having a reading
8 center or having one person do all the analysis is very
9 important.

10 What's wrong with this analysis? Well, here's
11 an example of analysis done in this area, just localized
12 down in this area. Only 71 cells were counted, but it
13 still had an endothelial cell density of 2,639. So the
14 analysis really is not representative. It's introducing
15 bias because you're looking at a population of a lot of
16 small cells here, you're not likely to be able to repeat
17 this analysis, and really we say that you have not counted
18 enough cells.

19 It is very important to group the analysis like
20 this or as illustrated here, and when you look at your
21 grouping analysis, notice the box that we've drawn here.
22 This is an improper grouping that you would see here
23 because you're doing this nearest neighbor analysis as the
24 algorithm of the speculoscope and may only end up with 50
25 cells or something like this, whereas if you group the

1 whole group, you'd end up at least putting a dot in 150
2 cells. But see, technicians have to be trained if they're
3 going to do this, or your reading center.

4 Patients that have guttata. You may have some
5 of these in a study group, grouping here, here, here, or
6 here.

7 DR. BULLIMORE: This is Mark Bullimore. Excuse
8 me interrupting. You've talked about guttata twice and you
9 seem to infer that you should count around them when
10 estimating cell density.

11 DR. EDELHAUSER: Right.

12 DR. BULLIMORE: So you don't include that area
13 at all in your analysis, even though there are no cells
14 there.

15 DR. EDELHAUSER: Well, there's just usually one
16 large cell that covers that area, but we have found that in
17 doing patients like that, if they're part of the study
18 group, the best analysis is to just use the cells without
19 including that guttae in there. The reason is is that if
20 you put that one large cell, you're multiplying this by
21 such a large factor that your cell number is extremely
22 variable. See, you're wedded to the algorithm of the
23 specular microscope.

24 DR. BULLIMORE: Thank you.

25 DR. EDELHAUSER: And hopefully, in doing a

1 study, you would not have many of these patients in there,
2 but I can tell you from the studies that we have done with
3 LASIK and things, you do find some patients that do have
4 guttata.

5 To analyze the cells, you need to be able to
6 visualize the cells. You have to identify a pattern. And
7 would it be appropriate to take this endothelial cell that
8 has shown some damage?

9 Where the image is analyzed can create a great
10 degree of variability, as illustrated here. The old way
11 which we used to do specular microscopy with contact
12 specular microscopy is take a wide field and then we'd have
13 to trace the corneal endothelial cells, put a number in,
14 and then we would digitize each one of the corners. This
15 is very accurate, but again, notice the grouping of the
16 cells.

17 Here are examples of variability. This is one
18 specular image here. If you analyze the endothelial cells
19 in the lower portion, you'd up with a cell density of
20 2,976. If you analyze the endothelial cell density in the
21 upper portion, you'd end up with a cell density of 2,873, a
22 difference of 103 cells and a 4 percent difference. So you
23 can see the variability that can occur and this can very
24 easily occur if the training of that individual is not
25 appropriate.

1 Here are examples of variability within
2 readers, and this occurred out at our center when we were
3 training the people out of our Vision Correction Center to
4 do this. Endothelial cell density 2,531 here and 2,358
5 here, a 7 percent difference just on the same pattern.

6 Here are examples of variability between
7 readers, with having different readers. So in this case,
8 we had five different readers put dots in each one of the
9 cells, and you can see they varied from 2,531 up to 2,631.
10 So this is really a degree of variability. So training not
11 only needs to occur with the photographer, but also the
12 person doing the analysis.

13 Just to show you this, the consequences of
14 overcounting, if you skip two cells, you have a significant
15 difference. If you overcount three cells, you have a
16 significant difference. So this is where the training is
17 extremely important for the individuals.

18 Well, just to put this into a little
19 perspective on this, and this is a graph that we've
20 recently put together, the first study that was done that
21 we did back with Richard Yee, et al., this is what happens
22 with contact specular microscopy. Notice, from age groups
23 from 10 up to 89. Notice, this is the distribution of
24 endothelial cells here.

25 Okay. We recently went back and did 125

1 patients through the various decades with the non-contact
2 robo, which is illustrated in the yellow line, and notice
3 that the lines overlap. Very early, we published a paper
4 in the AJO and I took the preoperative data from our LASIK
5 patients, which varied from 20 to 50, and notice those
6 lines overlap.

7 There are two areas of outliers, and this was a
8 mixed Asian group of patients that we had in Emory when we
9 looked at this, and notice the Asian patients have a higher
10 endothelial cell density, and a number of years ago we had
11 access to a Japanese population in Osaka when Dr. Matsuda
12 was with us, and in this population, notice that the
13 Japanese population in Osaka had many more endothelial
14 cells than a Caucasian American.

15 So this becomes a very interesting point of
16 view when one wants to look at endothelial cells in grouped
17 patients if you're doing a study, say, in the West Coast
18 compared to, say, in the South or the Midwest.

19 Mike?

20 DR. GRIMMETT: Just a quick question. I hope
21 you don't mind the interruption.

22 DR. EDELHAUSER: No, not at all.

23 DR. GRIMMETT: The non-contact robo data, is
24 that published somewhere? Is that an abstract?

25 DR. EDELHAUSER: No, that's published, Mike.

1 That's the original data from Richard Yee's paper we
2 published in Current Eye Research.

3 DR. GRIMMETT: In '85.

4 DR. EDELHAUSER: In 1985, yes.

5 DR. GRIMMETT: Is there an updated one?

6 DR. EDELHAUSER: No, that's not published yet.

7 DR. GRIMMETT: Oh, I see.

8 DR. EDELHAUSER: It's in the process of being
9 written up. We just completed that within about two months
10 ago.

11 DR. GRIMMETT: Thank you.

12 DR. EDELHAUSER: But I thought it was a very
13 interesting comparison because much of the data in the
14 literature is from the contact scope, and this is really
15 the first longitudinal study with the non-contact.

16 Just to give you an example of the variability
17 in the best of hands, this was taken from our LASIK paper,
18 where Ramzy Azar took all of the photographs of the
19 patients, and he then used his own eye throughout a three-
20 month time period where he took the pictures of his right
21 eye and his left eye. So this is 36 different photos, 18
22 of the OD and 18 of the OS. His endothelial cell density
23 is 2,545 and 2,600.

24 Notice the standard deviation, 45 cells. So
25 the precision in the best of hands with this, and this is

1 from this AJO paper, is 1.7 percent and 1.5 percent.
2 That's with one person looking and taking all the photos,
3 and I think this is very important.

4 A recent study that we've done and reported at
5 ARVO, which I think is very important as we think about the
6 endothelial cells, we measure central endothelial cells,
7 but peripheral endothelial cells are going to become of
8 interest, too, particularly when you think about phakic
9 IOLs.

10 These are three graphs where lyserine red-
11 stained human corneas, something like 71 human corneas that
12 we looked at. You can see the N listed here. This line is
13 the endothelial cell density in the center, the paracenter,
14 and the far periphery, about 4.5 millimeters from center.
15 You can see there is a progressive decrease of roughly a
16 half a percent per year all the way across the line, but
17 still you do have a higher cell density in the periphery
18 that could aid in the sliding of endothelial cells to the
19 periphery.

20 So just to summarize this, then, what are the
21 sources of variability? It's difficult to return to the
22 same location. When we were a reading center for
23 KeraVision, we did a reproducibility study with 10 patients
24 at three different sites where they took three consecutive
25 readings, and we ended up plus or minus 56 cells, very

1 similar to what we measured in the LASIK study. So you
2 have an inherent error, just the reproducibility, of 2
3 percent.

4 Poor image quality. We suggest trying to get
5 at least 100 cells.

6 Training error. Training, and you have to have
7 consistency. Reading analysis. Training and consistency,
8 and equipment calibration and alignment is another very
9 important issue that has to be.

10 So in summary, what the ideal situation might
11 be is it could be a company, it could be an independent
12 reading center, it could be you need your specular sites,
13 and this data then should be sent to a reading center. You
14 should not have the sites do their own analysis. Then the
15 data in a mass fashion, which would be received to the
16 reading center, would be sent to the data processing
17 center, and then for statistical analysis then to the
18 technology company, and obviously then on to the FDA.

19 So I hope this little bit of a summary was
20 important and I was able to show you some of the
21 variability of the technique. It's a good measurement,
22 it's a hard measurement to get, and what is very important
23 is that you do certainly want to see what the state of the
24 corneal endothelium is.

25 Thank you for your attention.

1 DR. WEISS: I'd like to thank you both for
2 excellent presentations. Perhaps you could come up to the
3 table and the panel could start their questions.

4 I would just like to ask you a couple of
5 elementary ones. What would you suggest as the minimal
6 time of follow-up in order to detect endothelial cell loss
7 after phakic IOL implantation? So what's the shortest
8 study?

9 DR. EDELHAUSER: Well, I think certainly a
10 three-month time period, that's a reasonable approach to
11 take it. I mean, are you trying to say how soon after --

12 DR. WEISS: Two years, three years, five years?
13 What would your wish list be?

14 DR. McCAREY: If the literature is any
15 indicator, I would imagine that the most active changes are
16 going to occur probably within the first six months, and
17 then afterwards you're probably going to level out into
18 some kind of a steady effect. So the initial trauma of the
19 procedure, let's say the first six months you need the
20 data. Afterwards, you might need data every six months for
21 maybe two years, and then hopefully you're going to see
22 some kind of a level line that you're dealing with. If you
23 don't, you're just going to have to go further.

24 DR. WEISS: So just to clarify if I understand
25 you correctly, you would say two and a half years from

1 implantation?

2 DR. McCAREY: Certainly two years.

3 DR. WEISS: Two years from implantation as a
4 minimal, unless there is anything else that you can tell.

5 DR. McCAREY: Correct.

6 DR. WEISS: If a patient is a contact lens
7 wearer before, that's an evolution of what is occurring
8 with the endothelium as well. Before they have their
9 phakic IOL, how long should they be out of contact lenses
10 so you get a stable specular microscopy before they can be
11 entered into a study?

12 DR. McCAREY: Yes. That's almost a
13 presentation on its own as to how the patient is able to
14 return from this polymegethism state from contact lens
15 wear. It looks like it's very, very, very slow, if at all,
16 there is a correction from that polymegethism change. So
17 it means that you could look at a patient one, two, three
18 years, five years out of having not wearing their contact
19 lenses and they would still have the effect of wearing the
20 contact lenses.

21 The next part of the issue is does this mean
22 that the eye is a little susceptible to further trauma?
23 And the literature would indicate that these eyes are more
24 susceptible to trauma. They respond more negatively to
25 trauma than a person who had a normal CV and no contact

1 lens history.

2 DR. WEISS: So should that be an exclusion
3 criteria then?

4 DR. EDELHAUSER: No, I wouldn't think so. It
5 shouldn't be an exclusion criteria if somebody has
6 polymegethism.

7 DR. WEISS: No, I mean contact lens wear,
8 because it sounds like it's such a confounding variable
9 that you --

10 DR. EDELHAUSER: It is, but I think there is
11 variability within the degree of polymegethism because if
12 you're thinking of phakic IOLs and everything, basically
13 all these people have worn contact lenses.

14 DR. McCAREY: I agree with Dr. Edelhauser.
15 That's the problem. You're going to lose an awful lot of
16 your patients.

17 The second part of the story about
18 polymegethism is it's a stress from oxygen. If you are an
19 old-fashioned PMMA lens wearer, you have the most stress.
20 If you have the more modern, let's say the silicone
21 materials or a high-water content hydrogel, you'll probably
22 have less stress. So it's a sliding scale as to how much
23 stress they have had from their contact lenses.

24 I think what I want to point out is that the
25 endothelial cell density is not alone an indicator as to

1 the history of that patient. You'd also want to know
2 what's going on with their CV, the spread in the cell
3 sizes, and I think good data collection is probably more
4 important a statement than eliminating these patients.

5 DR. WEISS: If I had to put you on a spot and
6 ask you to give a bare minimum -- not the range, but the
7 bare minimum -- you think that someone would have to be out
8 of contact lenses, would you be able to give me a number?

9 DR. McCAREY: It would just be a wild number
10 and I would certainly --

11 DR. WEISS: A wild number might still be
12 helpful.

13 DR. McCAREY: Certainly six months, but I don't
14 really know for sure.

15 DR. WEISS: Okay. Six months.

16 Would Asian corneas then have to be grouped
17 differently because they're starting out with more
18 endothelial cells?

19 DR. EDELHAUSER: I would think that would be a
20 subset that should be analyzed separately. From past
21 experience with that, all Asians that we've looked at have
22 a very higher cell density, and it depends upon where the
23 study is going to be conducted, but I wouldn't use an
24 exclusion. I'd just use it as an added subset.

25 DR. WEISS: A subset. Thank you very much.

1 DR. McCAREY: Could I add one more thing on
2 this?

3 DR. WEISS: Yes.

4 DR. McCAREY: I think that the contralateral
5 eye is a goldmine, that a lot of these issues that you're
6 referring to can be lessened as far as you're concerned if
7 you know the history of the contralateral eye. Follow both
8 eyes and make the data relevant within the patient
9 themselves, rather than some kind of a standard regression
10 line from a group. I think will solve a lot of problems.

11 DR. WEISS: So in this case, you would suggest,
12 at least from the endothelial cell portion, that it would
13 be very helpful only to do unilateral phakic IOL surgery.

14 DR. McCAREY: Yes. Unfortunately, that's what
15 I would state.

16 DR. WEISS: Thank you.

17 We're going to go around. Dr. McCarley, then
18 Dr. Burns, then Dr. Bullimore, Dr. Matoba, Dr. Grimmett,
19 and then we'll go on down the line.

20 MR. McCARLEY: This is Rick McCarley. I knew
21 if I waited around long enough, I'd get a degree, too. So
22 thank you.

23 (Laughter.)

24 MR. McCARLEY: It's just Rick.

25 DR. WEISS: I think I'm going to start with

1 first names and go back to the first names.

2 (Laughter.)

3 MR. McCARLEY: There you go. Thank you.

4 You'll see my eyebrows going up several times
5 today because obviously I'm involved in a clinical study on
6 phakic intraocular lenses in the U.S. that's been going for
7 about five years now, and in fact 15 years in Europe. So I
8 have a lot of -- I'll call it practical experience, and
9 boy, I wish I knew then what I know now. We do have a lot
10 of data and I wanted to share some of this because it
11 applies to all of us. These discussions have happened in
12 the ANSI standards, so I'm pretty well up to date on what
13 has happened in the industry and what data we've collected.

14 But a couple of the comments, one is the
15 patients not only wear contacts. Most of these patients
16 that we've seen have polymegethism, but many of them, we're
17 talking about -15 to -20.

18 DR. WEISS: Actually, I'm going to interrupt
19 you for a moment. Because of the time constraints, what
20 I'd like to do is use the benefits of our experts'
21 expertise, and I would prefer the comments get directed to
22 the comment portion.

23 MR. McCARLEY: That's okay.

24 DR. WEISS: And if you have any questions to
25 direct to Dr. McCarey or Dr. Edelhauser, use this time for

1 that.

2 MR. McCARLEY: Okay. Then I will ask the
3 question directly. Have you ever studied a population of
4 high myopes individually and compared that to the normal
5 population?

6 DR. EDELHAUSER: No, we haven't. The only high
7 myopes that we've really looked at were part of our study
8 that we published on LASIK, where had 100 consecutive
9 patients that we looked at and there were only, I think,
10 eight to 10 at the most that were high myopes.

11 MR. McCARLEY: I see. And when you're
12 analyzing the endothelial cell data over a large
13 population, the comment about the subgroup of Asian eyes,
14 are we looking at percent changes, so it really doesn't
15 matter what their beginning or ending is? So looking at a
16 subgroup really doesn't matter. If they start off with
17 more, we'd expect them to end up with more.

18 DR. EDELHAUSER: I think that's how the study
19 design is set up and how the statistical analysis is done.

20 MR. McCARLEY: Right.

21 DR. EDELHAUSER: I mean, as an independent
22 reading center, we want to be masked in that. So the
23 criteria would be in the early study design and how you're
24 going to do that.

25 MR. McCARLEY: Thank you.

1 DR. WEISS: Dr. Bandeen-Roche?

2 DR. BANDEEN-ROCHE: Yes, I have maybe three
3 related questions. The first one is both of you alluded to
4 cell density not being uniform over the surface of the eye.
5 Would you think it would be worth some sort of a dynamic
6 sampling strategy to try to isolate the maximum cell loss
7 or is that relatively reliable in the center? I'd just
8 appreciate your thoughts on that.

9 DR. MCCAREY: I think you'd be opening up a can
10 of worms if you approached it that way. I think you're
11 probably best trying to get central readings, and with
12 instruments like the Konan, hopefully the patient can
13 cooperate and look at the target and you're getting the
14 same field.

15 On my own eye, I could take 10 pictures, and
16 every one of us having slightly different patterns and you
17 can see an odd cell here and there, and within the 10
18 pictures, I could see the same little couple of cells. I
19 can come back two or three months later and do that again
20 and once again see those same little odd cells.

21 So I think that the key here is training and
22 cooperation from the patient and the central cells, and
23 that gets rid of some other cans of worms.

24 DR. BANDEEN-ROCHE: Thank you.

25 DR. EDELHAUSER: Let me just add one other

1 thing. I think in order to get a representative, it is
2 recommended, and we certainly have recommended this, that
3 if you're going to take specular photographs, at least try
4 and get three photographs, and then at least have the
5 reading center or whoever is doing the analysis try and
6 then analyze the best one of this, or in the early training
7 of your individual, if you have them take three, and then
8 take the average to see where they are. So again, it comes
9 back to teaching the photographer to get a representative
10 photo.

11 DR. BANDEEN-ROCHE: Thank you.

12 The second question goes to variability over
13 repeated readings, say, over a three-month time period, and
14 you alluded to in the best case percentage variability of
15 1.7 and 1.5 percent. I'm curious. How much of that is
16 variability in the reader versus natural variability in
17 cell density over three months? And when you refer to
18 those rates being the best, I tend to say, well, suppose
19 somebody just counted more cells? Couldn't it get better?
20 If you could respond to that.

21 DR. EDELHAUSER: In this particular case, I say
22 it was the best because we had one person taking the
23 pictures of his eye and counting as many cells as possible
24 to come up to do this, and I think that what you're dealing
25 with in this particular case is the variability of the

1 machine and the algorithm. Because don't forget, in this
2 particular case, you're, say, dotting 150 cells. At best,
3 160 maybe is all you can put on there. Then you push the
4 button and the algorithm pops up here, and what you're
5 dealing with is that's what you're left with, the analysis
6 of those particular cells that you're dealing with.

7 DR. McCAREY: I kind of take a little bit
8 different approach to that. I think the math is the math.
9 It's not changing. The computer's not changing. The
10 machine is hopefully focusing the same and keeping the same
11 magnification. So your variation isn't in the equipment.
12 It's in either where the picture was taken -- well, that's
13 probably the heart of it, where the picture was taken,
14 because there is a variation across the surface.

15 Now, you mentioned the best answer and the
16 worst. I showed you 9 percent of a spread in order to get
17 all the patients in the group. That's with seven clinical
18 sites, 58 patients, and no expectation that I was going to
19 do that analysis. That's the hardcore reality.

20 Whenever you look at a paper that comes from a
21 given site -- whoever it may be, our lab or Bill Bourne's
22 or someone else's -- they are doing the entire study
23 themselves. They are giving you their best shot. They
24 know they're going to do the study, and it always comes out
25 cleaner that way. So my 9 percent is probably reality and

1 the equipment probably is as good as 1 percent.

2 DR. BANDEEN-ROCHE: Thank you, and a very brief
3 final question that goes to guttata. So the point of not
4 counting that, I take it that induced guttata is not a
5 primary problem in phakic IOLs?

6 DR. EDELHAUSER: Provided it doesn't cover the
7 whole surface of the corneal endothelium. I mean, we've
8 all seen patients that have guttata that go from limbus to
9 limbus, and then occasionally you'll have a person who will
10 sit down and you'll get one guttae in the area. I mean,
11 you still can use that photograph. So I think there are
12 various degrees.

13 DR. WEISS: Thank you.

14 Dr. Burns, did you have some questions?

15 DR. BURNS: Yes, two. Steve Burns. Two simple
16 questions.

17 First, is it true that if you take, say, three
18 sets of images that the one with the highest count is best?
19 I thought I heard you say that, but I might have
20 misinterpreted it.

21 DR. EDELHAUSER: No, I think you the best image
22 that I was implying is the one where you have a good
23 distribution of cells over the whole screen that you can
24 see, and not one where a patient may have moved their eye a
25 little bit and you only get a strip of the endothelial

1 cells. So the best image that I would suggest would be one
2 that has as many cells uniform across the full screen.

3 DR. BURNS: So given that you've got three good
4 images, do you just average them? Do you recommend
5 averaging those counts for that data point?

6 DR. EDELHAUSER: Yes, yes.

7 DR. BURNS: The second question is when you
8 were talking about how long you'd follow up, was that sort
9 of in laboratory-type data or were you taking into account
10 the realities of variance from a trial? So the two and a
11 half years you were suggesting, do you think you'd have to
12 lengthen that given the variability you get from a
13 multisite study?

14 DR. EDELHAUSER: You might. The best
15 illustration I'd give you is our LASIK data, and we looked
16 at this very carefully for 100 patients and we followed
17 them up to three years. Of the 100 patients, we able to
18 get 63 of them back -- again, this is all volunteer at this
19 particular stage -- and we really found no change over a
20 three-year time frame. But I think with something that has
21 the potential where endothelial cell populations may be
22 decreasing, going out to two or three years might be
23 important.

24 DR. WEISS: Dr. Bullimore?

25 DR. BULLIMORE: Mark Bullimore. I'd like to

1 thank both of you for coming. It's a fabulous presentation
2 and it's very encouraging for those of us who do clinical
3 research in general to see the level of rigor with the
4 reading center. I mean, that was very refreshing.

5 We took some data on the Konan probably under
6 the worst-case scenario, and our precision was probably
7 closer to 10 percent than 2 percent, but we weren't
8 counting the number of cells and we weren't doing all the
9 other sophisticated things that you gentlemen do.

10 I have hopefully a couple of quick questions.
11 First of all, when you talk about coefficient of variation
12 that's what other people, or maybe yourselves, would also
13 refer to as polymegethism? Are those two terms equivalent
14 or interchangeable?

15 The other thing is, and this is a particular
16 concern given the fact that many of the patients having
17 phakic IOLs will be long-term contact lens wearer, you
18 inferred or implied that if you take a patient out of
19 contact lenses, there would ultimately be a very slow or
20 potentially no long-term recovery from that insult. Did I
21 hear you correct?

22 DR. MCCAREY: That's strictly from the
23 literature. It's not from my own laboratory experience,
24 but Brian Holden has done lots of work in this area, and it
25 repeatedly shows up that that's true.

1 DR. BULLIMORE: So taking that to the next
2 step, were we at some future date to be looking at these
3 data, you would not worry about that contact lens or prior
4 contact lens wear as a confounding factor in any changes in
5 endothelial count that occurred after the patient had a
6 surgery?

7 DR. McCAREY: There is literature out there
8 that tells you that large polymegethism values often lead
9 to a patient being more susceptible to the trauma of a
10 given surgery as compared to patients with a lower
11 coefficient of variation. So they do have the potential to
12 be more susceptible to damage.

13 DR. BULLIMORE: I see, but that's a short-term
14 effect of the surgery, rather than their sort of five-year
15 history, say.

16 DR. McCAREY: I don't really know if it would
17 mean that the five- and 10-year periods would still be at a
18 higher rate of loss or not. I don't know.

19 DR. BULLIMORE: Did you want to go ahead?

20 DR. EDELHAUSER: There may actually be a
21 benefit of removing the contact lens because I say from our
22 experience, in our three-year data from the LASIK patients,
23 we actually did see an improvement in the coefficient of
24 variation, and all these patients were contact lens
25 wearers.

1 DR. BULLIMORE: And a final question. There
2 has been a great deal of emphasis on your slides and in
3 other materials I've looked at on the topic on endothelial
4 cell density. Do you think that should be the primary
5 outcome measure or should we be looking at coefficient of
6 variation as the primary outcome measure in a long-term
7 study or would you consider both to have equal weight?

8 DR. EDELHAUSER: I think cell density would be
9 the number one aspect of it. The difficulty with the
10 coefficient of variation that we have if you use the robo,
11 to some extent that data is a little soft, and the reason I
12 say that is soft is because you're using the center dot
13 method. If you were tracing cells and using the corner
14 method, that data is much stronger.

15 One of the things that I have found over the
16 years of using the robo, if you have a patient or a subject
17 that has a high coefficient of variation -- say, .6, or
18 like many of the diabetic patients -- it shows up, but the
19 difference between .27 and .35 is not really a significant
20 change.

21 DR. BULLIMORE: So without wanting to put words
22 in your mouth, the precision of the coefficient of
23 variation method is not particularly -- let me rephrase
24 that. The precision of the coefficient of variation
25 measure is not particularly impressive.

1 DR. McCAREY: Well, the coefficient of
2 variation, I passed the slide very quickly, but the
3 calculation is that you're dividing the mean cell area into
4 the standard deviation or the spread in that mean cell
5 area. So I feel that it is a piece of informative
6 information, but you do get a lot of noise, though, in it
7 from the fact that there is a spread in the data. I'd
8 personally like to see that information carried forth in
9 the study.

10 DR. BULLIMORE: I lied, Madam Chairman. I do
11 have another question.

12 I'm very familiar with a paper by Scott McCray
13 on long-term PMMA contact lens wear, where he looked at a
14 cohort of patients who'd worn PMMA lenses for 20 years and
15 reported their outcomes, and one of the things I found
16 compelling about the paper is actually, and it's not
17 emphasized in the paper, but the cell density in the
18 contact lens wearers centrally was actually higher than the
19 controls.

20 Okay? The take-home message was that there was
21 this subset of patients who fell below a given value of
22 cell density. I think it was nine out of the 81 contact
23 lens wearers compared to two of the controls, which was
24 statistically significant.

25 So in his analysis, and using that as, if you

1 like, an analogy to what we're doing here with phakic IOLs,
2 would it not be more appropriate, rather than emphasizing
3 the mean endothelial cell density, to look at sort of, for
4 want of a better phrase, incident cases of significant or
5 substantial reductions in cell density? Have you explored
6 that parameter yourselves or is it in the literature?

7 DR. EDELHAUSER: It's not in the literature,
8 but in the database that KeraVision submitted to the FDA, I
9 know it's there because they went back and looked very
10 significantly at patients who may have lost greater than 10
11 percent of their cells, and they were reported.

12 The other interesting thing in that paper
13 you're referring to by Dr. McCray, of that subset of
14 patients, there were a group of contact lens wearers who
15 actually lost cells.

16 DR. BULLIMORE: Yes. That was my point, and it
17 was nine out of the 81 were way below what you might
18 consider the normal range, but when you actually averaged
19 the cell density --

20 DR. EDELHAUSER: It was lost.

21 DR. BULLIMORE: It was lost. So I think we
22 should maybe keep that in mind.

23 DR. MCCAREY: When you get polymegethism, you
24 actually appear to be getting smaller cells, not just
25 losing cells and big ones reappear. That would be a

1 misconception. There's actually an appearance of what
2 appear to be smaller cells. Recently, and I unfortunately
3 don't know the author, there was a description of how this
4 occurs.

5 DR. BULLIMORE: That was Michael Delaty,
6 probably.

7 DR. McCAREY: I don't remember, but he has
8 certainly has a lot of articles.

9 You can actually see a triangular-like pattern
10 occurring and that triangle shows a smaller top to the
11 aqueous, what looks like a smaller cell. The volume of the
12 cell may be the same. So there is a shift in the
13 dimensions of cells, rather than a loss of cells.

14 DR. BULLIMORE: Sort of from a cylindrical
15 profile to a trapezoidal.

16 DR. McCAREY: Right, and so it appears that
17 they could have a very high cell density when that's really
18 true if you counted the whole number of cells across the
19 surface.

20 DR. BULLIMORE: Thank you both again. This has
21 been very, very helpful.

22 DR. WEISS: Thank you.

23 Dr. Matoba, did you have questions?

24 And I will again reiterate, because we're
25 already going to be off time and running over. So if the

1 members of the panel could make their questions short and
2 sweet and directed to the issue at hand, I'd appreciate it.

3 DR. MATOBA: Do you want us to identify
4 ourselves?

5 DR. WEISS: Yes. I mean, we can identify
6 ourselves for the first time around, and then I think the
7 transcriptionist won't have a problem.

8 DR. MATOBA: Okay. Alice Matoba. My question
9 is your presentation indicated that there are significant
10 differences between races in terms of endothelial cell
11 density, and I wonder if you have any sense whether there
12 can also be differences between races in terms of the
13 minimum endothelial cell count you would need before one
14 starts to develop clinical edema?

15 DR. EDELHAUSER: I don't think that's in the
16 literature at all. I mean, just as a little bit of a
17 sidelight, if you go back and looked at the original radial
18 keratotomy, it was done by Sado, and the reason he was
19 somewhat successful I think is that the population of
20 individuals he did the study on had more endothelial cells.
21 So no, we don't know the minimum, and the best data would
22 probably come from Japan, Dr. Matsuda's laboratory.

23 DR. WEISS: Dr. Grimmatt?

24 DR. GRIMMETT: Dr. Grimmatt. My question was
25 asked by Dr. Bandeen-Roche and answered, so I'll pass at

1 this time.

2 DR. WEISS: I'm just going to ask you a quick
3 follow-up question, then. I understand that you would want
4 CV as part of specular microscopic studies. Is there a
5 number that you would assign beyond which this is of
6 concern? I'm being a very concrete person.

7 DR. EDELHAUSER: Are you talking about an upper
8 level?

9 DR. WEISS: Upper level, yes.

10 DR. EDELHAUSER: Well, the thing that you see
11 in your upper levels are CVs up around, say, 45 and above.
12 You know, that's a very high number.

13 DR. WEISS: That's of concern.

14 DR. EDELHAUSER: Yes.

15 DR. WEISS: Thank you.

16 Dr. Bradley?

17 DR. BRADLEY: Dr. Bradley. A couple of
18 statistical questions, really. You seem to be suggesting
19 you should be avoiding contact lens wearers in the sense
20 that I got the impression you were treating that as perhaps
21 a confounding source of an independent variability, but if
22 the contact lens wear interacts with the effects of phakic
23 IOLs, are you then more susceptible to this? And these are
24 the sorts of patients that might be getting phakic IOLs.
25 Surely, they shouldn't be excluded, but should they be

1 specifically included in such a study? Could you comment
2 on that?

3 DR. McCAREY: I agree completely with what
4 you've said. I just want to make sure that you're aware of
5 which patients has had a contact lens history.

6 DR. BRADLEY: Second question. Again, I think
7 statistically you did quite a thorough job of demonstrating
8 different sources of variance, and I lost track a little
9 bit of the individual sources of the variance, but it
10 seemed you put that all together in a graph and you
11 suggested that in order to detect a change in cell density
12 in an individual eye, it would have to change by 9 percent.

13 DR. McCAREY: With that set of data that I
14 presented to you, yes.

15 DR. BRADLEY: So the question, and I wondered
16 if you knew the answer, is what would be the sample size
17 required to detect a clinically significant change in the
18 sample of eyes that might be used, for example, in the
19 study of phakic IOLs?

20 DR. McCAREY: I'd have to go back to the
21 computer. I don't know the answer. It's a statistical
22 question that I didn't ask.

23 DR. GRIMMETT: Michael Grimmatt. I'll present
24 that during my talk.

25 DR. WEISS: Dr. Huang?

1 DR. HUANG: Andrew Huang. My question is that
2 so far we have emphasized the physical characteristics of
3 the endothelium, but we all know corneal thickness is a
4 function of the corneal endothelial functions. Do the
5 speakers have any thought about what's the value of corneal
6 thickness in terms of evaluating the cornea's general
7 health?

8 DR. McCAREY: Well, as part of an answer, and
9 I'm sure Dr. Edelhauser can expand on this, but you can get
10 endothelial cell counts down below 1,000 to 900 and 500 and
11 still have normal corneal endothelial thickness.

12 DR. HUANG: Exactly, yes.

13 DR. McCAREY: So it seems to be not as
14 sensitive an indicator as to what trauma may have happened
15 to that tissue.

16 DR. HUANG: But by the same token, the flipside
17 of the coin is that if you have a decrease of cell density
18 from your graph, from the aging population, from 3,000 or
19 4,000 at birth to 2,000, but the patient did not really
20 have any functional visual disturbance, is that a bad thing
21 to have a decrease in those endothelial cells or is that a
22 good thing to have a healthy corneal thickness?

23 DR. EDELHAUSER: Well, I think there's a limit
24 obviously. I mean, a corneal endothelial cell population
25 between, say, 1,000 and 2,000 will survive very nicely,

1 because we see this in many cases with patients with
2 guttata and we see it with postkeratoplasty with patients
3 and it's fine.

4 I think that obviously when you set up a study
5 that you want to do this where there's a potential loss of
6 endothelial cells or you want to see it, you don't want to
7 start out with patients that have 1,400 cells, for example.
8 So you'd really want to have -- a "normal" endothelial cell
9 population with some polymegathism would be fine, up around
10 2,500 cells per se.

11 DR. HUANG: But by the same token, you may now
12 have started with the patient in, say, the Asian population
13 with an endothelial cell count of 2,500, but with a corneal
14 thickness of thicker than 600 microns.

15 DR. EDELHAUSER: Occasionally, yes, you do see.
16 Some people do have thicker corneas.

17 DR. HUANG: But that itself may be indicative
18 of the corneal endothelium is compromising.

19 DR. EDELHAUSER: I understand. Sure. That's
20 true, very much so.

21 DR. HUANG: Yes. Seeing the cell number does
22 not necessarily mean the cell is alive.

23 DR. EDELHAUSER: Right, but I think you bring
24 up, if corneal thickness is going to be an issue, again,
25 that's another training point, and, one, the corneal

1 thickness measurements off of some of the specular
2 microscopes are not that accurate compared to ultrasound.

3 DR. WEISS: Dr. Mathers?

4 DR. MATHERS: Presumably, you would recommend
5 that we do not include patients with Fuch's dystrophy and
6 significant guttata because that would confound this
7 measurement considerably, correct?

8 DR. EDELHAUSER: Yes.

9 DR. MATHERS: But you see an occasional
10 guttata, maybe one or something like this, in a fairly
11 large percentage of the population. Could you hazard a
12 guess as to how many in single field could be there and you
13 would qualify them to be excluded?

14 DR. McCAREY: Well, as a reader of the images,
15 it isn't so much if they're present. It's can I get a
16 large enough area remaining that's contiguous for counting
17 of the cells. So I do not count around the cells, and I
18 don't want to count a narrow sheet between guttata because
19 that will louse up the algorithm.

20 DR. MATHERS: But to do this study, you want to
21 have as clean a group as possible. So presumably, we
22 wouldn't want to have patients where we're fighting the
23 guttata.

24 DR. McCAREY: Yes. This is probably one of the
25 reasons I like to see more than one picture taken because

1 if there is a random guttata, I try to select the picture
2 with the least problem.

3 DR. MATHERS: So you're not going to --

4 DR. McCAREY: Rather than averaging the three.
5 That's not so important to me because I think that when you
6 consider the surface area, it's .003 percent of the surface
7 for one picture. What's one more picture out of the whole
8 surface? Very little.

9 DR. MATHERS: Yes, right.

10 DR. McCAREY: But you want to get a good
11 picture, and if it means getting a good contiguous field of
12 cells, then that's what a good picture is.

13 DR. MATHERS: All right.

14 DR. WEISS: I get the impression that Dr.
15 Mathers is trying to quantify it because we're doing a
16 guidance document.

17 DR. MATHERS: Yes, right, because if you take
18 enough pictures, you're going to get a spot where you can
19 count 150 cells and in a single field you might still have
20 15 guttata. We may not want to include this in a study
21 where we're looking at this because those guttata are going
22 to indicate a confounding population. We need some kind of
23 measure as to say this person has too many guttata to
24 include in a study like this.

25 DR. EDELHAUSER: In a preops study, yes. I

1 mean, I think that this could be an exclusion criteria.

2 DR. MATHERS: Right.

3 DR. EDELHAUSER: And that would be put in
4 there. You know, obviously, there are patients that have
5 few guttata, but there are a lot of patients that have a
6 lot of guttata and they should be excluded.

7 DR. MATHERS: Okay. We'll call it a lot.

8 And presumably, when you suggested a two-year
9 follow-up, you're speaking of an insult and then a process
10 of evaluating the endothelium after that time, but if you
11 have an ongoing insult, ongoing inflammation, presumably
12 then would you modify your two-year recommendation if
13 you're going to assess that?

14 DR. EDELHAUSER: Indeed, I would. You know, if
15 you're going to follow these patients, three years
16 certainly would be reasonable to follow these patients out.

17 DR. McCAREY: Are you implying a chronic
18 inflammation?

19 DR. MATHERS: Chronic inflammation.

20 DR. McCAREY: If it was a chronic inflammation,
21 wouldn't you expect a chronic loss?

22 DR. MATHERS: Correct.

23 DR. McCAREY: So you would expect to see
24 eventually a linear line occurring, and that's when I'm
25 telling you that you've followed them long enough. You

1 don't have to follow them infinitum. You need to know
2 what's going on at a steady state.

3 DR. MATHERS: Right, but that would presumably
4 be longer than an initial insult period study. So you were
5 asked to give an estimate and when you said two years,
6 certainly that would be longer if you have a chronic
7 process. Can you give a time?

8 DR. McCAREY: I still kind of flip the response
9 back to you by saying that I'm looking for a linear
10 response.

11 DR. MATHERS: Yes.

12 DR. McCAREY: And if it's still not linear at
13 the end of two years, I have to keep going. I have to go
14 for a longer follow-up time.

15 DR. MATHERS: Right, but we need --

16 DR. McCAREY: And I would not know how long it
17 would be.

18 DR. MATHERS: You don't know.

19 DR. McCAREY: Yes.

20 DR. MATHERS: Okay. Fine.

21 DR. EDELHAUSER: I think, Dr. Mathers, the
22 longest study that we've followed through are the LASIK
23 patients, and that's been three years out.

24 DR. MATHERS: Right.

25 DR. EDELHAUSER: So I haven't really

1 participated and I think with the KeraVision, their three-
2 year data is just now coming in and being analyzed.

3 DR. WEISS: Dr. Owsley?

4 DR. OWSLEY: Cynthia Owsley. Dr. McCarey, you
5 mentioned that when people stop wearing their contact
6 lenses, the cell density counts, if we look at the
7 literature, suggest that it's pretty stable or there's not
8 this miraculous going back to the norm, whatever that is.
9 From the pragmatics of doing a clinical study on patients,
10 most of whom will be contact lens wearers and who have very
11 severe myopia, do you feel it's too burdensome on patients
12 to have them be without the contacts for six months and is
13 that maybe a little inflated? I mean, I know they can do
14 the spectacles, but being a myope myself, I know that a lot
15 of contact lens wearers, they like to wear their contacts
16 and not the spectacles. Just in terms of patient
17 enrollment issues.

18 DR. MCCAREY: I have a great answer for that.
19 I'm a Ph.D. I don't have to worry about the clinical part.
20 I really don't know how to answer you because --

21 (Laughter.)

22 DR. OWSLEY: That's a good answer.

23 DR. WEISS: Dr. Swanson, did you have any
24 questions?

25 DR. SWANSON: No questions at this time.

1 DR. WEISS: Great.

2 I want to thank you both very much. Those were
3 excellent presentations and extremely helpful to us, and I
4 thank you for your good humor with putting up with our
5 questions as well.

6 So you can move back from the table if you
7 would like, and we next have Dr. Liliana Werner from the
8 Storm Eye Institute, who will be speaking to us on lens
9 opacity.

10 Donna, do you have something to say first?

11 MS. LOCHNER: I'd just like to introduce Dr.
12 Werner a little more formally. She is an assistant
13 professor of ophthalmology at the Storm Eye Institute at
14 the Medical University of South Carolina in Charleston.
15 She is the senior scientist of the Center for Research on
16 Ocular Therapeutics and Biodevices.

17 She received her doctor of medicine from the
18 faculty of medicine of the Federal University of Minas
19 Gerais in Brazil in 1989, her residency in ophthalmology at
20 the Felicio Rocho Hospital in Brazil, and two postresidency
21 programs at the University of Paris and the Hotel-Dieu
22 Hospital in Paris. In 1999, she received a Ph.D. from the
23 University of Paris and began her work at the Storm Eye
24 Institute.

25 She is editor, together with David J. Apple, of

1 the summer 2001 issue of the International Ophthalmology
2 Clinics and is currently serving as a scientific referee
3 for many ophthalmology journals. She was recently selected
4 to joint the International Intraocular Implant Club and
5 starting in September of 2002, she will be the director of
6 research of the new David J. Apple Laboratories for
7 Ophthalmic Devices Research at the John Moran Eye Center at
8 the University of Utah in Salt Lake City.

9 Thank you.

10 DR. WERNER: Good morning. I would like first
11 of all to thank the FDA members for the opportunity to be
12 here and participate in this meeting, and I will be
13 discussing the issue of cataract formation after
14 implantation of phakic posterior chamber intraocular
15 lenses. This presentation is based on a review of the
16 literature, but also on some studies we performed in our
17 center and, as mentioned, soon we'll be moving back to Salt
18 Lake City, where the center was in fact founded in the '80s
19 by Dr. Apple and Dr. Olson.

20 So in fact what we did is an update of the
21 report we prepared for the ANSI meeting in Newport Beach
22 last year, and I would like to start with a brief overview
23 of the cell types involved in the problem of crystalline
24 lens and capsular bag opacification.

25 So if you look at this picture, we can in fact

1 divide the crystalline lens epithelium into two different
2 biological zones, and in this zone we have the A-cells, and
3 these cells are attached to the inner surface of the
4 anterior capsule, and when the cells are disturbed, they
5 have the tendency to remain in place and undergo a process
6 of fibrous metaplasia. These cells are in continuity with
7 the cells in the equatorial region, or the E-cells, and
8 these cells, on the contrary, when they are disturbed, they
9 have the tendency to migrate and proliferate, forming
10 bloated cells.

11 So both cell types are involved in the
12 different forms of capsular bag opacification. For
13 example, anterior capsular opacification after implantation
14 of different intraocular lenses. Also, different forms of
15 secondary anterior to capsular cataracts. Also,
16 interlenticular opacification between piggyback lenses, and
17 finally posterior capsular opacification after implantation
18 of different intraocular lenses.

19 So here, for example, you have the A-cells
20 being the most important cell type involved in the process
21 of anterior capsular opacification after implantation of
22 different intraocular lenses for cataract surgery, and you
23 can see here a beautiful example of the anterior capsule
24 being opacified only where it's in contact with the IOL
25 material.

1 So here you have another example, and this is a
2 case of capsule contraction syndrome, and because you have
3 asymmetric fibrotic formation and asymmetric contraction,
4 the lens is also decentered.

5 Whenever you prepare those specimens for
6 histopathological evaluation, that's what you're going to
7 find at the level of the capsule axis edge. So there are
8 always these fibrocellular tissue attached to the inner
9 surface of the anterior capsule, and this in fact
10 corresponds to the opacification in this border.

11 And of course, the A-cells are also the cell
12 type most involved in the anterior capsular cataract
13 associated with phakic IOL implantation, and here I have a
14 bilateral case provided by Dr. Koch. So we have here the
15 opacity in the right eye and in the left eye. I'll be
16 talking a lot today about the ICL because the available
17 literature is related to the ICL and also these are the
18 specimens we have available to us in our center.

19 So what happens in this case is that the
20 surgeon has to explant the lens and then he is going to
21 perform the cataract procedure. So we are recommending
22 them to save for us the capsule excess fragment so we can
23 perform histopathological analysis of this anterior capsule
24 fragment, and in fact it's been very interesting to notice
25 that there are many similarities between anterior capsule

1 specimens obtained in different situations.

2 So for example, here you have the capsule
3 excess edge of a case of anterior capsular opacification
4 after implantation of a silicone lens, here you have the
5 specimen, the capsule excess specimen obtained during the
6 surgery of an anterior subcapsular cataract secondary to
7 uveitis, and finally here is the specimen we received in
8 our center. It's the capsule excess obtained during the
9 cataract procedure for a case of anterior subcapsular
10 cataract after phakic IOL implantation. So in fact, if you
11 see these three examples, you will always find this
12 fibrocellular tissue attached to the inner surface of the
13 anterior capsule, corresponding to the opacification.

14 Finally, the E-cells are the most important
15 cells involved in the process of posterior capsule
16 opacification and mostly in the pearl form of posterior
17 capsule opacification. Both cells, and mostly the E-cells,
18 are involved in the process of interlenticular
19 opacification between piggyback lenses, and when you
20 analyze such specimens in histopathology, you are going to
21 find residual corneal material and pearls very similarly to
22 what is observed with posterior capsular opacification.

23 I'd like now just to summarize the evolution of
24 the designs of the phakic posterior chamber lenses.

25 So, as you know, these lenses were introduced

1 by Fyodorov in the '80s and the first designs were pupil-
2 fixated lenses. So this lens, for example, was supposed to
3 stay in the sulcus, but the optic component would protrude
4 through the anterior chamber through the pupil.

5 The second generation was represented by the
6 Chiron Adatomed silicone lens, and in fact this lens was
7 withdrawn from the market because of cataract formation.
8 This was really a very thick lens.

9 Finally, the third and current generation is
10 represented by the Staar ICL manufactured from the collagen
11 material. This is a much thinner lens, and in fact there
12 are different models of this design and each model has
13 different vaulting characteristics.

14 The third generation is also represented by the
15 Medennium phakic refractive lens, or PRL, manufactured from
16 silicone, and this is also a very thin lens, and you have
17 here the myopic model and the hyperopic model.

18 So let's talk about some relevant aspects of
19 fixation and sizing. We had the opportunity to analyze
20 some Chiron Adatomed silicone lenses which were explanted
21 because of the problem of cataract formation. Then, after
22 analysis of the lenses, we reimplanted the lenses in eyes
23 of different sizes, and in fact we could observe from the
24 posterior view or a side view that the lens was really too
25 big and too thick. The lens was really sitting on the

1 zonulas. We could not fixate the lens in the sulcus, and
2 because it was very thick, it was in large contact with the
3 posterior surface of the iris and anterior surface of the
4 crystalline lens.

5 With respect to the ICL, consecutive V models
6 of this design had different vaulting characteristics, and
7 this was done in order to reduce the possibility of
8 cataractogenesis. Apparently, the sizing is important for
9 this design. So a lens that's too large will be followed
10 by excessive vaulting, but a lens that's too small for the
11 eye will be unstable and eventually become decentered.

12 Dr. Ferdinand Trinidad from Brazil very nicely
13 summarized different situations with incorrect sizing of
14 the ICL. So for example, if you have a lens that's
15 oversized, the vaulting will be excessive and there will be
16 a large area of contact between the lens and the posterior
17 surface of the iris.

18 Here, for example, there is a central vault,
19 but a large mid-peripheral contact, and you have a pool of
20 aqueous humor that's stagnated between the lens and the
21 crystalline lens, and eventually, as we're going to discuss
22 further, there is the possibility of some metabolic
23 disturbances.

24 Finally, if the lens is clearly undersized, the
25 lens will be unstable and there will be a large area of

1 contact between the lens and the anterior surface of the
2 crystalline lens.

3 So the sizing issue is eventually a very
4 important issue for phakic IOL implantation in general, and
5 in general surgeons are using the measurement of the white
6 to white to finally choose the size of the lens that's
7 going to be implanted in the eye of the patient.

8 For example, for the ICL, if you review the
9 literature, surgeons would measure the white to white and
10 then add 0.5 millimeters for a myopic eye or they subtract
11 0.5 millimeters for a hyperopic eye, but this measurement
12 can be so inaccurate, and sometimes we receive some cadaver
13 eyes in our lab and we don't even know exactly where to
14 measure.

15 This is a very recently published paper by this
16 group. They analyzed 43 eyes of 24 patients. They
17 patients were aged at around 34 years and they were highly
18 myopic or hyperopic. They performed measurements of the
19 white to white with surgical calipers, and they tried to
20 look for a correlation between the white to white and the
21 sulcus diameter measured with composites of UBM
22 photographs.

23 They concluded that the traditional estimation
24 of the sulcus size through the limbal measurement is
25 inadequate. So the limbus size alone would not be able to

1 predict the sulcus size.

2 We are also trying to do different studies
3 using cadaver eyes regarding the sizing. For example, we
4 are actually working on this protocol where we get
5 different cadaver eyes, we measure the anterior/posterior
6 length, then we mark the 12 o'clock position, and we
7 localize the horizontal meridian and the vertical meridian.
8 Also, we perform measurements using a plastic sizer of the
9 anterior chamber diameter, and after that we try to fixate
10 the eye with special techniques which allow us to keep the
11 geometry of the whole anterior segment. Then we select the
12 meridian to be studied with the form sections, and then we
13 directly measure the angle to angle and the sulcus to
14 sulcus with surgical calipers.

15 So in fact, we have some eyes where we studied
16 the vertical meridian and other eyes where we studied the
17 horizontal meridian, and this is preliminary data and the
18 study is not finished, but it's already very interesting to
19 notice that, for example, here, for the same measurement of
20 the white to white, which here is 11, we obtained real
21 measurements of the sulcus to sulcus which went from 11 to
22 almost 13. So then if you would choose an 11.5 ICL to
23 implant in these eyes, what would happen with the eyes
24 between 12 and 13?

25 So I would like to mention the new technology

1 that's being developed that will help in the issue of the
2 sizing, and I mention this device because this is the
3 device we are having the opportunity to work with right
4 now.

5 So we are working this protocol where again we
6 use cadaver eyes and we measure the anterior/posterior
7 length, then we mark the 12 o'clock position, measure the
8 white to white, and with this prototype of ultrasound we
9 are performing of the anterior chamber diameter and then
10 the sulcus-to-sulcus diameter. Then we prepare the eye
11 with these special techniques for fixation. We perform the
12 sections in the region we choose, and finally we perform
13 the direct measurements of angle to angle and sulcus to
14 sulcus.

15 This is also preliminary data, but so far we
16 analyzed nine phakic cadaver eyes, and if you compare the
17 angle-to-angle measure by calipers and ultrasound, the
18 results are very similar and this is valid also for the
19 sulcus to sulcus, and this is also valid for pseudophakic
20 cadaver eyes we analyzed. So far, we analyzed only six.

21 When you look at the pictures you obtain with
22 the ultrasound, in fact they apparently reflect very nicely
23 the morphology we obtain after the fixation of the
24 specimen, which allows us to perform the measurement which
25 appeared to be very accurate. So here you have an example

1 of a phakic cadaver eye, and here the same analysis is
2 performed in the pseudophakic cadaver eye.

3 Of course, this technology is going to be
4 extremely important in the follow-up of patients implanted
5 with different phakic IOLs. It will be important for the
6 measurement of the distance between the edge of the lens
7 and the mid-periphery of the cornea. For example, in the
8 phakic anterior chamber intraocular lenses, and also
9 extremely important to the measurements of the posterior
10 surface of the lens and the anterior surface of the
11 crystalline lens in phakic posterior chamber IOLs.

12 So let us review briefly the surgical
13 implantation. We have to remind you there are lots of
14 opportunities for the surgeon to create the cataract
15 observed in the postoperative period.

16 So the first thing the surgeon has to do is in
17 fact to perform these YAG laser iridotomies. In general,
18 they use two superior iridotomies placed 90 degrees apart,
19 and this is performed one or two weeks before surgery.
20 There are some studies indicating that these have
21 eventually a cataractogenic effect also and that they
22 contribute to pigment deposition which we always observe on
23 the surface of these lenses. Also, in an alternative way,
24 the surgeon can perform one single surgical iridectomy.

25 After that, the surgeon has to perform the

1 incision. These are foldable lenses, the incision is very
2 small, and it can be used to correct preexisting
3 astigmatism. The surgeon has to inject viscoelastics,
4 which is extremely important in the protection of
5 intraocular tissues and also to allow the lens to unfold in
6 very controlled manner.

7 Both lens types can be inserted with forceps
8 and also injected within the anterior chamber, and then
9 finally the haptics will be placed behind the iris with
10 spatulas or hooks, and this is a very important step
11 because no pressure should be placed on the crystalline
12 lens at that time. Then the pupil is constricted with
13 miotic agents, the viscoelastic is removed, and the wound
14 is closed.

15 So of course, the crystalline lens should
16 ideally not be touched at all during the whole surgery, but
17 as you can see, there are many opportunities to have
18 accidental contact with the anterior capsule of the
19 crystalline lens not only during the placement of the
20 haptics behind the iris, but also injection of viscoelastic
21 behind the iris, et cetera. So anterior capsule trauma, as
22 we review the literature, you will notice that this may
23 lead to crystalline lens opacities months later after the
24 procedure.

25 There are some studies indicating that in many

1 ways high myopic patients are going to have cataract and
2 with earlier onset. For example, I can cite this study
3 indicating that moderate to high myopic patients had an
4 association with age-related cataract. For lower levels of
5 myopia, this relationship has been disputed. They also
6 indicated that early onset of myopia is a strong
7 independent risk factor for cataract.

8 But we can not forget that they are talking
9 here about age-related cataract. They are talking about
10 mostly nuclear cataract, and when you review the different
11 forms of cataract according to the age they appear, you're
12 going to notice that anterior subcapsular cataracts are
13 very rare forms of age-related cataract unless they are
14 caused by inflammation or injury.

15 So I'd like to summarize some of the specimens
16 we are receiving in our center. We had the opportunity, as
17 I mentioned, to analyze some silicone Chiron Adatomed
18 lenses and we have recently received eight ICLs, all
19 explanted because of cataract formation. There are some
20 bilateral cases and the lenses were explanted between one
21 year and four years after implantation.

22 Here you have some examples. This is one of
23 the eyes of the patient, and here the corresponding ICL
24 explanted from this eye, and this is the contralateral eye
25 and the corresponding ICL explanted from the eye. So this

1 surgeon not only submitted the ICL he explanted, but also
2 he submitted the fragment of capsular excess while he
3 performed the cataract surgery.

4 So in general, when you analyze the surfaces of
5 these ICLs, you always find some pigment deposition, as you
6 can observe here, and in these specimens, stained with
7 different techniques, you always can observe the
8 fibrocellular tissue attached to the inner surface of the
9 anterior capsule which is corresponding to the opacity.

10 This pigment deposition can be very discrete,
11 as in the previous case, but it can also be very important,
12 as you can see here in this bilateral case. These lenses
13 were also explanted because of cataract.

14 What about the mechanisms of this cataract
15 formation? This study is very interesting because it
16 summarized many of the factors that are eventually
17 important. So these patients were implanted with the ICL
18 and they observed an anterior chamber reduction in 9 to 12
19 percent of the cases. Central endothelial cell density
20 decrease, not progressive, but very interesting, they
21 report an increase of the aqueous flare in 50 percent of
22 the cases with stabilization, but always above preoperative
23 values. They reported progressive decrease of crystalline
24 lens transmittance with time, contact ICL iris in all eyes,
25 peripheral contact ICL and crystalline lens in 60 percent

1 of the cases, central contact of the ICL and crystalline
2 lens in 15 percent of the cases, and changes in ICL axis in
3 10 percent of the cases with rotation of the lens in the
4 postoperative period. But they didn't observe any cataract
5 formation after the follow-up.

6 So of course, we mentioned already surgical
7 trauma can cause these cataracts were are observing after
8 implantation of phakic lenses. We cannot forget the
9 possible effect of the YAG laser for the iridotomy. We
10 cannot forget the accidental contact of the anterior
11 capsule is possible during different surgical steps.
12 Intermittent microtraumas can also cause these cataracts.
13 There is an increased crystalline lens curvature during
14 efforts for accommodation. It was demonstrated that the
15 lens can rotate inside the eye in the postoperative period,
16 and of course, there is always an increase in the overall
17 lens size throughout life, so the distance between the
18 phakic lens and the crystalline lens is not always going to
19 be the same.

20 So what about constant trauma? This apparently
21 is extremely important. So here in cases of clearly
22 undersized lenses, there would be a large area of contact
23 between the lens and the anterior surface of the
24 crystalline lens.

25 Also, there is the possibility of a continuous

1 disruption of the blood/aqueous barrier with subclinical
2 inflammation, and this is caused by friction between the
3 iris and the phakic lens, and eventually by the ciliary
4 sulcus fixation also. These have effects not only on the
5 crystalline lens transmittance, but eventually on the
6 corneal endothelium.

7 What about crystalline lens metabolic and
8 nutritional disturbances? We already commented on this
9 situation, for example. There is a pool of aqueous humor
10 stagnated between the lens and the anterior surface of the
11 natural crystalline lens. So this could be caused by the
12 previously mentioned subclinical inflammation, but by any
13 cause of blockage of normal circulation of the aqueous
14 humor.

15 When we reviewed the literature, in fact we
16 performed a review from '96 to 2002, and we could only find
17 studies regarding the early Fyodorov lenses, the Chiron
18 Adatomed silicone lenses, and the ICLs. We could not find
19 any studies regarding the PRL. I'd like to comment on some
20 of these studies because they have very interesting points
21 which are eventually very important.

22 So for example, in this study of patients
23 implanted with the Chiron Adatomed silicone lens, there was
24 no space between the phakic lens and the natural
25 crystalline lens in all cataract cases, which places

1 eventually this factor as one of the most important
2 factors.

3 In this study by Zaldivar and coworkers and
4 studying patients implanted in the ICL, he reported one eye
5 with a peripheral anterior subcapsular opacity which
6 developed in the region of the peripheral laser iridotomy,
7 showing again that these iridotomies eventually have a
8 cataractogenic effect.

9 So this group in Brazil studying patients
10 implanted with the Staar ICL reported an anterior
11 subcapsular opacity in the central non-contact area. So
12 the contact eventually is very important, but maybe there
13 are other factors or maybe the follow-up was just not
14 enough.

15 This group, also studying patients implanted
16 with the ICL, reported anterior subcapsular opacity which
17 developed 24 hours after surgery. So we may think that
18 this was really caused during the surgery and not by the
19 lens itself.

20 So this group reported one case of nuclear
21 cataract in a 53-year-old male. He had already some degree
22 of nuclear sclerosis, so of course, this is not the kind of
23 cataract we are talking about here. This is maybe just
24 age-related cataract and is not related to the procedure
25 and not to the lens also.

1 This is one of the very few studies which
2 really describes the evolution of the opacities. So they
3 describe opacities which appeared superiorly and then
4 progressed involving the optical zone, and in all cases
5 there was in fact a satisfactory central ICL vaulting in
6 the cases of cataract, indicating that in these particular
7 cataract cases, the contact was not the most important
8 factor. I like to cite this study because in general there
9 are many surgeons that would say that some peripheral
10 opacities would never progress.

11 Finally, this is maybe the only study which
12 compares patients implanted with an ICL in one eye and the
13 Chiron Adatomed silicone in the other eye, and they
14 demonstrated that the silicone lens was associated with
15 more cataracts and the cataracts appeared earlier in the
16 postoperative period. In all cases, no space was observed
17 between phakic lens and natural lens, so again, here we
18 believe that the contact is the most important factor.

19 So when you group all these papers together,
20 it's a big problem to really understand what is the real
21 incidence of cataract. With regards to the silicone lens,
22 the rates vary from 0 to 52.9 percent and regarding the
23 ICL, they go from 0 to 25 percent.

24 So why is that? First of all, because the
25 definition of cataract and opacity is really not the same,