Patient. Steep K is one.

DR. MAGUIRE: I am sorry, one other one -- I don't know if this is an issue anymore but flexion of the base of the keratome. I don't think this is a problem with the steel-based instruments but I think there is some scuttlebutt that there is some flexion with plastic and people are getting into trouble. I don't know if that needs to be an issue now or not.

DR. MCCULLEY: Well, I think it does because we are looking to the future as well. How can that be stated in the positive? Absence of flexion of the base, I guess? Base plate stability? Good. Base plate stability/rigidity -- not necessarily the appropriate word here but it gives the intent.

Other operator issues here? I mean, the operator clearly has to recognize the circumstances, as we said above, and make adjustments. So, in terms of operator, recognizing the situation and adjusting --

DR. MAGUIRE: One blade operator issue is measurement of intraocular pressure. That should be one. I will stop there unless you want an explanation.

DR. MCCULLEY: And that should go under one and two, that the operator must ensure appropriate obtaining of suction -- appropriate IOP.

DR. MAGUIRE: It is not measurement of; it is

confirmation of -- this isn't the right way to put it but confirmation of adequate IOP.

DR. MCCULLEY: It is adequate suction. That is what it is.

DR. REINSTEIN: And monitoring.

DR. MCCULLEY: Yes.

DR. REINSTEIN: Because you can check it and you have to continuously monitor it.

DR. MCCULLEY: Okay, so confirmation of adequate IOP and its maintenance. Dr. Higginbotham?

DR. HIGGINBOTHAM: I am going to try this again. I still think that, for instance, a patient characteristic is important as it relates to IOP, particularly if they have had previous surgery such as filtration surgery. I would think that would influence --

DR. MCCULLEY: That is a contraindication of the surgery.

DR. HIGGINBOTHAM: But in the marketplace --

DR. MCCULLEY: It is not done. I mean, if a patient has had previous filtering surgery -- previous intraocular surgery in general is an absolute contraindication for the procedure, except penetrative keratoplasty. Glaucoma filtering operation would be an absolute contraindication --

DR. HIGGINBOTHAM: Okay, because I know it has

been discussed.

DR. MCCULLEY: Not Lasik.

DR. HIGGINBOTHAM: Okay, I just thought I would ask.

DR. MCCULLEY: Good, good.

DR. MACRAE: This will get into the whole patient issue, if the anatomy is appropriate for surgery, whether they have had retinal detachment surgery or filter surgery, or they had some type of anatomical nuance -- that all falls under that category.

DR. MCCULLEY: Anything else under operator? What else, other than steep K under patient?

DR. REINSTEIN: Under operator, the operator needs to know the patient's case before he chooses the right ring. The operator needs to verify with the applanation lens before passing the keratome.

DR. MCCULLEY: Mitigating circumstances. I mean, those are solutions to it.

DR. REINSTEIN: They are possible causes of poor precision. It is incorrect selection of rings, of applanation --

DR. MCCULLEY: So, we can put under operator incorrect selection of patient or microkeratome characteristics.

MR. MASTEL: How about tremor?

DR. MCCULLEY: How about what?

MR. MASTEL: Tremor.

DR. MCCULLEY: None of us has that!

DR. MCCULLEY: So, under operator it really is appropriate patient and keratome selection.

DR. REINSTEIN: I am not sure if this would fit here but sterility of the device during --

DR. MCCULLEY: It doesn't fit under this.

DR. REINSTEIN: It doesn't? Okay.

DR. MCCULLEY: That is going to come under infection and debris.

DR. REINSTEIN: Okay.

DR. MACRAE: This is very basic but the operator really needs to assess the instrument before doing the pass. In other words, look at the blade and make sure that the blade is moving --

DR. MCCULLEY: Right, okay.

DR. MACRAE: -- there are certain elemental pieces to --

DR. MCCULLEY: Right. Mr. Bartell?

MR. BARTELL: If you are going to be looking at manual and automated I think you should put translation speed under operator potentially as coming up with inaccurate cuts because of the speed of the transition.

DR. MCCULLEY: Okay, yes, and we are looking at

automated and manual.

DR. PULIDO: It lists keratomes as being AC powered or battery powered devices --

DR. MCCULLEY: Or automated. Yes, they are manual. Maybe when we come to the document we need to make sure that that guideline document addresses manual as well as automated. Is your question are we addressing only automated and not manual?

DR. PULIDO: Correct.

DR. ROSENTHAL: [comment off microphone].

DR. MCCULLEY: My impression from what we have been directed is that we should be addressing automated as well as manual microkeratomes in this.

DR. BEERS: That is correct. Battery and AC relate to, for instance, blade oscillation where you still have power even for a manual.

DR. MCCULLEY: Then we can get into synchronous, and all that, but any other patient characteristics under this category? This is our toughest and probably, as Scott said, most important area. Any other patient characteristics, other than steep K that we are going to leave in there? Yes, Mr. Mastel?

MR. MASTEL: Would you include small eyes and large eyes like diameters here, or not?

DR. MCCULLEY: Patient corneal diameter. Good

point. Well, that is probably overall and all patient selection, operator. Let's just leave that under the broad category of appropriate patient selection by the operator.

DR. REINSTEIN: The only thing that the patient does to control the depth of the incision is to not sit still or to squeeze his lids or not be relaxed, altering the intraocular pressure during the procedure, to move so that the passage of the keratome isn't smooth. So, it really has to do with cooperation.

DR. MCCULLEY: Okay, can we put patient control and cooperation to cover it all? Doyle?

DR. STULTING: I was going to say I think the issue here is really a general one. It is the anatomy of the patient. As Dan pointed out earlier, it is how much stuff is sticking up through the hole when the blade comes by, and that has to do with the Ks. It has to do with the way the limbus is attached to the sclera. It has to do with the diameter of the cornea. It also has to do with the looseness of the conjunctiva, which is what the keratome attaches to. So there is really a huge number of factors. People talk about Ks, but that is just one of a number of factors, and I think what you ought to do is put here anatomy and move forward. When you move to cures, Dan mentioned a good one and that is the applanator because it takes care of all of them.

DR. MCCULLEY: So, patient anatomy which includes cornea, conjunctiva, sclera. It is important to consider all of those that we don't necessarily have good measures for. We find it out when we are putting the suction ring on.

Anything else under patient? If not, the next is quality of bed and perimeter, chatter lines, scoring, steps. Device. Clearly, an issue there relates to the appropriate and fine manufacture of the instrument but a specific is blade angle and oscillation speed.

MR. MASTEL: Blade characteristics again.

DR. MCCULLEY: Blade characteristics. What we might be able to say with that is kind of see all of the characteristics listed above where applicable rather than restating many of the same things again. Dan gave us a nice, long list of tolerances and characteristics that are going to enter in here. The blade angle, oscillation speed --

DR. STULTING: Translation speed.

DR. MCCULLEY: Translation speed -- let's see, we had translation speed above. I would say just see all of the above characteristics that we listed for number two. Any specific operator issues here with perimeter, chatter lines, and so forth? Certainly chatter lines with automated versus manual. Anything else?

DR. REINSTEIN: Under operator, translation control in manual keratomes.

DR. MCCULLEY: Thanks for watching that, Dan.

DR. YAROSS: Also blade reuse, again, would come in here.

DR. MCCULLEY: Good point.

DR. MAGUIRE: And also translation control in automated because you can certainly have wear and some maintenance issues come up.

DR. REINSTEIN: And there are some keratomes where you can actually tell the keratome how fast to go across. There are software modifications.

DR. MCCULLEY: Any other patient characteristics here? Any other surgical characteristics? Mr. Mastel?

MR. MASTEL: Wouldn't surgical skill and experience be a factor?

DR. MCCULLEY: We are not going to make that kind of judgment but we are going to say -- I think we have taken care of that with translational characteristics.

DR. YAROSS: But to Dr. Reinstein's point, appropriate selection of speed for blade advancement. So, that is really an operator issue, appropriate selection among the parameters of the instrument.

DR. REINSTEIN: I think that would be more a manufacturer dilemma because the interplay between oscillation speed and translation speed is what produces the chatter.

DR. YAROSS: Okay, I thought we were speaking to the selection amongst those that have variable choices.

DR. MCCULLEY: Well, but when there is variable you are going to have to match. I guess looking to the future, if we have the ability to adjust, other than with our manual translation speed, matching translational speed to oscillation rate. Mr. Bartell?

MR. BARTELL: Possible causes under operator is not really getting setting up properly. I think as far as scoring, hitting the speculum, which is really an observation that should be made prior to initiating any pass, is going to give you an irregular cut.

DR. MCCULLEY: So, operator would be avoidance of damage to microkeratome --

MR. BARTELL: And drapes and any other thing [comment off microphone].

DR. MCCULLEY: Can you put that in a few words that would cover the whole thing?

DR. MACRAE: I think a clear runway -- clearance, adequate clearance.

MR. MASTEL: How about inspection and maintenance?

DR. MCCULLEY: Who said that? Please say your name before you start.

MR. MASTEL: I am sorry, Doug Mastel. Inspection and maintenance.

DR. MACRAE: I agree, but when I think of inspection and maintenance I think of looking at the microkeratome under the microscope before I actually do my pass. I think clearance, for a clinician, captures that.

DR. MCCULLEY: Yes, well, they are both issues. As you said, we have to have a clear runway but we have to make sure the plane we are putting on the runway has been inspected and gone through a check list. I think that is what he was saying.

DR. MACRAE: I understand.

DR. MCCULLEY: Patient issues? Yes?

MS. HOANG: Did you want to add something in this column as to verifying the clearance?

DR. MCCULLEY: I am sorry, I had asked you to wait and we keep changing. Yes, put verification of -- let's just put in quotes clear runway and that the microkeratome has been appropriately inspected and its function verified.

DR. MACRAE: And adequate clearance?

DR. MCCULLEY: Well, that is what I meant by your clear runway. Mr. Bartell?

MR. BARTELL: Yes, patients with small eyes are particularly liable to cause the problems. I think that is something you should reference.

DR. MCCULLEY: Well, you know, there are tight lids, deep-set orbits, prominent brows. Let's just leave

that under appropriate anatomy and patient selection anatomy issues. Those are important anatomy issues.

DR. REINSTEIN: What really needs to go into that column is patient cooperation.

DR. MCCULLEY: Let's put ditto, that we have patient control and cooperation and patient anatomy. We did that before under item two above. We can bring that down. Any other patient issues?

[No response]

We are going to have to make a decision here. We are scheduled for lunch at 12:30. We can go till 1:00, I have been told. So, we will go till 1:00 and if we can complete this, we will. What I do not want us to is to fall into the trap of rushing through this stuff because I think that as we do this each column will get -- after we do this column, the next column should be easy as long as we don't embellish on our points.

The next item is epithelial ingrowth. Device related. I mean, I think the bevel is an issue. Did we have a nice, succinct summarizing term? I guess that came under bevel. It needs to be a clean cut that doesn't muck up the epithelium. So, absence of, you know -- kindness to epithelium on the part of the device. That relates to blade quality.

DR. MACRAE: This is a very complex area and for

us to try to describe all the components that give us a clean cut -- we all know what it is but it is a long discussion. So maybe we can just call it a good, clean cut and leave it at that.

DR. MCCULLEY: Clean cut and appropriate bevel.

DR. MACRAE: A lot of that is design related with all the different components.

DR. REINSTEIN: Probably the most important predictor of epithelial ingrowth is the presence of an epithelial defect after creating a flap. So, it is centered on that. So, stated in the negative, we would say lack of epithelial defect.

DR. MCCULLEY: So if we left it at clean cut, appropriate bevel or avoidance -- anyway, in the positive, clean cut, appropriate bevel, no epithelial defect that was contributed to by the microkeratome. Mr. Bartell?

MR. BARTELL: What bevel are you talking about? The bevel on the blade edge or the bevel --

DR. MCCULLEY: We are talking about the entry wound --

MR. BARTELL: The gutter.

DR. MCCULLEY: Well, you know, it depends on how you use the term. I think really what we are talking about is do we have a zero angle of cut into the cornea or do we have an angle cut into the cornea that does, indeed, create

a gutter as opposed to just a slice that floats. And, that is good. I think most of us up here knew what we were talking about, but it you guys don't and everyone doesn't, then we are not being effective. So, thank you for bringing that up.

Anything else on microkeratomes? Operator? Appropriate flap alignment, you know, covers, to me, the majority of it.

DR. REINSTEIN: Preoperative diagnosis of anterior corneal disorders like basement-membrane disease.

DR. MACRAE: In terms of epithelial ingrowth, I think the operator can have a huge impact on the epithelium. We have learned a lot over the last two or three years in terms of having good hydration throughout the procedure, keeping the epithelium moist, things like celluvisc and keeping the microkeratome well lubricated at the time of pass, and those things are quite critical and if you make a nice, clean pass generally without tilting the microkeratome you will get a good result. So, this is a very operator dependent issue usually.

DR. MCCULLEY: Okay, let me try and summarize what I think I have heard everyone say. The operator must keep the epithelium well lubricated and not traumatize it; that there needs to be appropriate flap alignment and seating; and that epithelial defects, when present, must be

appropriately managed -- appropriate management of epithelial defects. Doyle?

DR. STULTING: We have data for two things, one is epithelial defects which you already mentioned, the second is the removal of fluid from beneath the flap when it is replaced, and that is part of alignment so I think you can generalize that to say flap replacement technique. That includes alignment, removal of fluid, etc.

DR. MCCULLEY: Yes, the words I used were alignment and seating.

DR. STULTING: But it is specifically removal of fluid.

DR. MCCULLEY: That comes under seating, to me, but okay. If that would not cover it in the minds of people, then we need to put flap alignment, removal of interface fluid --

DR. STULTING: And put removal in quotes. It is indirectly done.

DR. MCCULLEY: -- and seating. Then the management of epithelial defects, when present, is, as has been pointed out, key in keeping the epithelium healthy. Anything else under operator?

DR. REINSTEIN: Detection -- immediate postoperative detection of epithelial plaques.

DR. MCCULLEY: That is postop. I agree with you in

the management and so forth of it that the sooner the better.

DR. MACRAE: I agree. Generally you can inspect the flap bed and see -- if you have an epithelial defect you can see usually that there is a piece of epithelium, or whatever --

DR. MCCULLEY: Right. So, in that context, yes. Immediate inspection at the conclusion of the procedure to be certain that there are not obvious epithelial tags tucked or plugs seeded.

DR. STULTING: It would be my opinion that the usual causes, the most frequent causes of epithelial defect do not include dragging epithelium underneath the flap by the microkeratome or its blade. If there is agreement of that, it might be worthwhile to say that specifically because that is something that has been discussed, and certainly the agency might be interested.

DR. MCCULLEY: I don't know whether that is appropriate or not. It would be opinion. Of course, all of this is opinion. I would agree with you that it is not. The biggest problems are when they communicate to the periphery either because there is a defect there or because a tag has been tucked under. Mr. Mastel?

MR. MASTEL: I think seeding is not what you want in that context.

DR. MCCULLEY: What word do I want?

MR. MASTEL: Seating.

DR. MCCULLEY: Oh, seating, yes. I did make it sound like seeding. It is my Texanese!

DR. MACRAE: While we are changing that, I just want to sort of editorialize because I know that this helps the agency, the epithelial ingrowth, in my experience, is mostly operator driven. So, at least in my clinical experience and in talking with other clinicians, most of these are caused by somehow epithelium getting in the interface, and usually it is related to some epithelium literally being dragged into the interface or some other reason. I haven't heard it as being a common problem as a result of a microkeratome.

DR. MCCULLEY: Well, if the microkeratome gets a bad bevel, it does. If the microkeratome leads to epithelial defects at the border, it does. I think if the blades are reused, it potentially does. So I think it does.

DR. REINSTEIN: And what is fascinating and has been shown by a good statistical prospective study is that even a central epithelial defect, which is nowhere near the wound, is a risk factor for epithelial ingrowth.

DR. MCCULLEY: Okay. Patient characteristics -- as has already been stated, clearly, avoidance of patients with anterior membrane dystrophy.

DR. MAGUIRE: Previous corneal surgery.

DR. MCCULLEY: Anything else under patient?

MR. BARTELL: Rubbing of eyes.

DR. MCCULLEY: Yes, slippage or displacement of the flap and rubbing. How should we put that? Rubbing leads to -- let's just say flap dislocation under patient. It is not always just rubbing. There are many times when it is also dry-eye patients that have a tendency to displace, more so. We will put it under flap dislocation issues. Dr. Higginbotham?

DR. HIGGINBOTHAM: You said dry eyes. What about systemic diseases -- diabetes, rheumatoid arthritis? Are they contraindicated too?

DR. MCCULLEY: I don't know that those would contribute to epithelial ingrowth.

DR. HIGGINBOTHAM: But you mentioned epithelial defects. It falls into patient selection and anatomy but it goes beyond.

DR. MCCULLEY: Well, systemic diseases that would cause dry eyes --

DR. HIGGINBOTHAM: Plus menopausal women, all those things.

DR. MCCULLEY: I don't know about postmenopausal women. Mr. Mastel?

MR. MASTEL: Does it have anything to do with,

like, the contact lens bandage, patching or not patching?

DR. MCCULLEY: We put under operator appropriate management of epithelial defects. That is where the bandaged one would fall. So we have that covered.

DR. ROSENTHAL: What about previous surgery?

DR. MCCULLEY: If a patient had RK before and there are epithelial plugs, keratoplasty, and so forth, yes, that increase the risk for it happening.

Let's go on to flap dislocation, slippage, poor alignment can result in wrinkles, microfolds, cracks, irregular astigmatism. Device issues here? These really are mostly operator and patient related.

DR. MACRAE: This area is a little bit of a mystery to me. I want to be educated from other people. But I do notice a difference between using the ACS in terms of my rate of flap wrinkles and microstriae and things like that compared to when I use a hand set.

DR. MCCULLEY: Which one being more?

DR. MACRAE: In the hand set I see microstriae very, very infrequently and the flaps are much more stable. So, I think there is an issue where one microkeratome may be creating a different incidence of these types of events than another microkeratome. It may be related to using a thicker microkeratome plate.

DR. ROSENTHAL: Dr. McCulley, I would rather you

not discuss specific instruments. You can discuss issues relating to them without naming them but this is not a place where we are comparing and contrasting various types of equipment.

DR. MCCULLEY: Thank you, point taken by everyone. Can we put under device, in quotes, creation of a stable flap? Then there would be characteristics -- is a thinner or a thicker flap more or less stable; more apt to have wrinkles? The amount of tissue that we have removed, I don't know that that relates to the flap -- the characteristics of the ablation bed as it relates to the flap. I am not sure how we get at this, other than the nebulous confusing that, you know, we need stable flaps, whether the hinge location, flap thickness, diameter, how they relate -- I don't know that we know the answer to it but we would like to have it.

DR. REINSTEIN: I agree. The flap bevel relates to how stable the manhole cover is in the manhole, and the flap thickness relates to the surgeon's ability to control it. Thinner flaps are much more difficult to control than thicker ones but they are more desirable for the patient's long-term safety.

DR. MCCULLEY: If we summarize that, it could be creation of a stable flap that relates to bevel, thickness, diameter and relationship to ablation bed.

DR. STULTING: And hinge placement.

DR. MCCULLEY: And hinge placement, yes. Now, under operator, it is going to be appropriate behavior to create what we have already said for the microkeratome. It is taking into consideration the characteristics that we are going to ask the microkeratome to do to create a stable flap. So from hinge placement, to thickness, to diameter to seating in the bed.

Are you going to make me say it again? You have all the issues that we had for characteristics of a stable flap that relate to the microkeratome. So it basically is surgeon behavior to complement what we have asked the microkeratome to do -- in eloquent words.

DR. SUGAR: And amount of ablation or depth of tissue removed.

DR. MCCULLEY: I tried to cover that by the relationship to the ablation bed. Did that not get up there? I had creation of a stable flap, bevel, thickness, diameter, hinge placement in relationship to the ablation bed, and then surgeon behavior to help to accomplish that. Patient characteristics are going to be similar to those that we had for epithelial ingrowth really.

DR. REINSTEIN: Under surgeon for flap dislocation, it appears that amount of hydration by the surgeon can affect the stability. So the amount of irrigation --

DR. MCCULLEY: So, maintenance of appropriate flap and bed hydration.

DR. REINSTEIN: Or ensuring that there is a proper stick from flap to bed.

DR. MCCULLEY: Confirmation of flap adhesion. Infection?

DR. STULTING: One other comment, we think tear deficiency, keratoconjunctivitis sicca is probably the best predictor of flap dislocation because the flaps dry out and get sticky. So that is a patient, surgeon, postoperative management issue that probably overrides most of the microkeratome issues.

DR. MCCULLEY: We had that under concerns with epithelial ingrowth and I wanted everything under epithelial ingrowth to be brought down to this area as well, which included the dry eyes.

DR. STULTING: I think it is different. For epithelial ingrowth the problem is that the epithelium gets knocked off. The flap becomes edematous and epithelium grows under it. For flap dislocation the problem is that the surface dries out even if the epithelium is there, and the flap becomes sticky and gets moved.

DR. MCCULLEY: I am not bringing down the explanation of the way it does it; I am bringing down the association of dry eyes under both. But I understand what

you are saying -- different mechanisms.

DR. REINSTEIN: The patient's behavior after the procedure affects wrinkles --

DR. MCCULLEY: Right.

DR. REINSTEIN: -- because if the patient does not consciously blink frequently, if the patient does not insert drops, it will dry the flap and cause --

DR. MCCULLEY: And they need not to rub. Mr. Mastel?

MR. MASTEL: Dr. McCulley, I would like to go back to what Dr. MacRae had brought up on the Ponsitilla --

DR. MCCULLEY: I am sorry, did you hear what Dr. Rosenthal said after Dr. MacRae did that and got his wrist slapped? We are not comparing machines. We are not comparing microkeratomes.

MR. MASTEL: Well, I am talking about blade physics. I don't care whatever --

DR. MCCULLEY: What I would ask is don't mention names --

MR. MASTEL: Okay, I apologize. A straight across microkeratome with a nasal hinge cuts when the chatter window goes straight lines, whereas the vertical devices cut in a mechanism that spans 90 degrees so you have a fan-tailing of the chop. It could be a factor in the wrinkles. I don't know; it is a theory.

DR. MCCULLEY: Okay. What are the two terms that best give a broad category? Track-and rail versus pivotal design. That is under flap slippage design, and that should probably also be under quality of bed questions and considerations.

DR. YAROSS: Then postop compliance.

DR. MCCULLEY: Okay, that is a good way to put it. So patient compliance with instructions.

Infection -- device. I mean, the obvious, appropriate sterility and maintenance thereof. Anything else under device relative to infection? The other point that was made before that, quite honestly, I never thought about -- I learn a lot every time I come to these meetings, but one was the possible association with infection in lid lacerations. So if that is agreed upon, the machine that tends to have a higher rate of lid lacerations theoretically might have a higher rate of infection. So, sterility assurance and maintenance, avoidance of lid lacerations relative to device. Then there are obvious things. I mean, if you have breaks in the epithelium and flap slippage then theoretically that would also increase risk for infection. Yes, Doyle?

DR. STULTING: First of all, the infection rates are so low that we really don't have any solid data but I think the record should reflect that, to me, it is the lid

lacerations is not the problem. The question is whether the microkeratome base and blade touch the lid, or whether it is designed in such a way that they touch surfaces that are likely not to be sterile so that they then bring whatever is on them into the bed. So, I think that is what the record show. Our concern is not simply the fact that we get lid lacerations.

DR. MCCULLEY: Yes, good point. Lid laceration would be an effect of what the problem is. Good point. So, assurance of non-contact of blade and keratome coming into contact with the cornea and not coming into contact with any other tissue.

Operator? I mean, the obvious maintenance of sterile technique. We could argue, and there are no data and never will be, appropriate use of prophylactic antibiotics.

DR. MACRAE: Previous corneal surgery and immunocompromise.

DR. MCCULLEY: So appropriate patient selection; beware of previous corneal surgery; beware of systemic diseases that would affect; beware of patient hygiene and presence or absence or concurrent local disease like blepharitis.

Patient would relate to what we have said with the operator needing to avoid.

DR. HIGGINBOTHAM: Appropriate use of medications.

Patients shouldn't touch the tip of the bottle to the lid.

DR. MCCULLEY: Patient compliance again.

DR. HIGGINBOTHAM: It goes beyond compliance.

DR. MCCULLEY: Okay, all right.

DR. HIGGINBOTHAM: Thank you.

DR. MCCULLEY: You win that one!

MR. BARTELL: How sterilizable are the devices? Some of these devices don't really need to be sterilized.

DR. MCCULLEY: Well, we put in the very first thing under device appropriate creation and maintenance of sterility. Would that not cover it? If you can't do it, then you flunk on that one. Dr. Pulido?

DR. PULIDO: Have you talked about bilateral use?

DR. MCCULLEY: We have not and we have left that where I would hope we would still leave it. It is not an FDA issue, and a practice of medicine issue. We have talked about reuse of blades though, which, you know, implies bilaterality.

DR. PULIDO: That is cause for an infection. I mean, if one has one eye with a problem --

DR. MCCULLEY: I understand your point and I understand not wanting to get into it, but I also understand that we have gotten into it. So, I am going to leave it, because of reuse of blades, that we have commented on it. I will leave it to Dr. Rosenthal to get us out of it.

DR. ROSENTHAL: Well, just before lunch, because it is one o'clock, Dr. McCulley, I thought I would inform the panel that the agency is addressing the issue of reuse of blades in single use instruments. It is doing it across the board in all the divisions, and it will be addressing this issue in our Division. That is all I can tell you right now. It is going to be a risk based approach, and I think I can say honestly we consider this a reasonably high risk. We will bring it to the attention of the committee in considering this issue. It is a major issue for the agency.

DR. MCCULLEY: Is that okay? It is a good point, Jose. Any other points on infection, because we need to break for lunch that was prepared for us? So, what we will do is break for lunch. If, in the interim, you can provide us hard copy for everything down to that point so you don't have to do it for everything; you only have to do it for the second half of it at the next break. Let's take 45 minutes for lunch. I have a couple of minutes after 1:00. Let's try and get back here and start up again at roughly 1:45. If there is a majority of people here, that is what we will do. So, if you are not here we will start without you.

[Whereupon, at 1:05 p.m., the proceedings were recessed, to be resumed at 1:450 p.m.]

AFTERNOON PROCEEDINGS

DR. MCCULLEY: Everyone should have a hard copy printout of the items that we have discussed so far. Put that aside for now, and we are going to pick up where we left off with interrupted movement, partial flap.

Let me also tell you that our agenda has been changed for us and the current plan is that what we will do is complete through causes and then go through the whole document again relative to mitigating events, and we will not do the scope of the proposed keratome guidance today. My impression is that the meat that we are providing to the FDA today they will use to create a draft -- a revised guidance document that we will then be asked to discuss at a later date.

We will maintain open discussion through causes and mitigating events, and then it will be just panel who will rank order. That does not include the public participation. Through mitigating circumstances, we ask still the public to actively participate.

MS. THORNTON: Just a point of order, Shirley McGarvey, you are taking Judy Gordon's place? Is that correct?

MS. MCGARVEY: That is correct.

MS. THORNTON: Could you give your name to the transcriber?

MS. MCGARVEY: My name is Shirley McGarvey. I am an regulatory consultant to Autonomous Technologies.

MS. THORNTON: Thank you.

DR. MCCULLEY: Same rules as before, before you start to speak please state your name, and if you have not yet spoken and it is your first time to enter into the discussion, state your affiliation and conflicts.

Let's begin with interrupted movement, partial flap. Device issues? I mean, we have the same things that we had before -- clear runway. I guess that is operator issue though, isn't it? Device? Anyone like to make a comment, statement on that? I mean, it clearly has to function reproducibly and go through its motions, and not jam, not stop, not be easily stopped with minor instructions. Anything beyond that? Scott?

DR. MACRAE: One question that I have, and this is more a question to the agency and to the microkeratome manufacturers, is how much of a tolerance there is for a partial occlusion? Let's say you have a particle that gets into the gears and slows it down, how much tolerance is there for something like that? Or, if the system has more friction on one of the units -- and I speak generically here, but on one of the units there is a system which reads out the amount of resistance in amps so that you know that the system is running smoothly, which is actually very

helpful, and we talk about the ideal situation but after a while these microkeratomes do run down and they probably do need maintenance. What kind of sort of a maintenance schedule do we keep with a microkeratome, and what is the tolerance in terms of when do we send these microkeratomes in for maintenance? It is kind of like driving a car, you know, when do you go and get a checkup? It would be helpful for the clinicians to have some kind of guidance from the manufacturers as to when is it inappropriate to be running your --

DR. MCCULLEY: That probably relates to a lot of the functions -- translational speed, as well as interruption of translation and oscillation of blade, and so forth. So, we probably want to put that as a broad issue, not just related to this one.

It seems to me, as a non-engineer, we are talking about drive force and how sensitive to interruption the drive is.

DR. MACRAE: Maybe to try and simplify this, we need a mechanism to determine whether the keratome is going to perform adequately in terms of the pass. Then, we also need some guidance from the manufacturers in terms of how to evaluate them.

DR. MCCULLEY: I guess the issue is what degree of interference would result in a stoppage, and do we have any

way of assessing or testing that, and I don't think we do.

DR. MACRAE: We don't. You know, right now the manufacturers -- it really depends upon your discussion with the manufacturers. We have microkeratomes running kind of slow; the amps are moving higher and higher; and we have a harder and harder time to get it to keep our amps down so that there isn't much resistance. Then the manufacturer says, well, send it in but we don't have much good guidance in terms of that. And, as the industry becomes more sophisticated -- it is almost like driving a car -- we want to have some type of guidance so that when a microkeratome is likely to fail it gets into maintenance before it does fail.

DR. MCCULLEY: I understand what you are saying, some guidance that if the amperage required to drive reaches a point that is a warning signal that the microkeratome needs its 30,000 mile check.

DR. MAGUIRE: I think what Scott is saying is that wear in a keratome can be keratome specific, and requires a specific proactive schedule maintenance. Instead of the keratome companies being reactive to a surgeon-identified problem, we need proactive scheduled maintenance specific for the wear of that keratome.

DR. MCCULLEY: Is that going to be number of cases or is it going to be performance characteristics of the

keratome that can be quantified?

DR. MAGUIRE: Well, when it is unclear what the wear of a keratome is, and when it is also unclear -- these are things we know: it is unclear how wear varies between keratomes by a specific company and between different companies' keratomes. It is also unclear how wear is affected by the expertise of the operator. So, when you are faced with lack of information you need to generate it proactively.

DR. MCCULLEY: And what I am saying is what do we want as our indicators that this is a time to have the microkeratome looked at by the manufacturer, sent in for a check?

DR. REINSTEIN: Perhaps as headings for that box we could divide the causes of interrupted movement to do with the device as to do with the motor drive or to do with the mechanics of the keratome. Because the motor drive needs to have sufficient torque to make the passage in different situations, and it has to have perhaps a feedback mechanism to increase the torque in situations where the torque may not be constant on a particular eye. There may be other issues inside the machine. Then at the level of the keratome on the eye, things that Scott mentioned -- debris in the track, lids in the way, speculum in the way -- events that can occur at the level of the eye that can make the passage

incomplete.

DR. MCCULLEY: Well, we have this -- device, operator, patient.

DR. REINSTEIN: Right, so in terms of the device we need to have perhaps feedback mechanisms that will enable the keratome to overcome resistance.

DR. YAROSS: Dr. McCulley, I think if we wanted to characterize the types of events we are talking about, they could be characterized as excessive wear, inadequate maintenance, inadequate torque, and then these issues as to how you would monitor those, those again get into mitigators. Potential mitigators could include things we discussed such as maintenance schedules --

DR. MCCULLEY: Good point. So we will come to that in a moment. Would you state then what the device issues are that relate to interrupted movement, partial flaps?

DR. YAROSS: So, the ones we discussed are excessive wear, inadequate maintenance and inadequate control of torque.

DR. MCCULLEY: Anyone have anything to add to that? No?

On operator we have the clear runway issue. Is there anything else on the operator side? What about patient? Patient cooperation I know is important because if the patient becomes uncooperative in the process then one

can end up with a jamming in the system.

DR. SACHAROFF: If I could just add a comment on the operator? Alex Sacharoff, Summit Technology. The cleaning of the microkeratome is quite critical to its optimal performance. So, I am concerned that this issue get raised and awareness be put to the panel that the surgeon and his staff plays a vital role in maintaining optimal performance of the microkeratome by maintaining it, and failure to do that can lead to problems.

DR. MCCULLEY: Okay. So, under operator would be appropriate maintenance --

DR. SACHAROFF: By the user.

DR. MCCULLEY: Appropriate maintenance and verification of function, regular verification of function.

DR. REINSTEIN: Under device we have mentioned electrical failure, lights out in the middle of a keratome passage. So, backup power systems. Under that, of course, backup IOP.

DR. MCCULLEY: Maintenance of suction, backup maintenance of power for the head, and then I guess -- it would come under irregular flap. I guess we have that somewhere further down, don't we? Yes. Disassociation of the two if one fails.

Anything under patient other than patient cooperation?

DR. MAGUIRE: Eyelid anatomy.

DR. MCCULLEY: Good point, patient anatomy.

DR. YAROSS: Actually, I think that was a good point, that the adequate maintenance may be moved over to the operator column.

DR. MCCULLEY: I think that is where we wanted it. That is where we had it -- oh, she put it in the wrong place? Everyone try to watch because she has a lot she is trying to do. So try to watch to make certain that what we are requesting is interpreted correctly.

DR. MAGUIRE: I think maintenance is a cooperative effort between the manufacturer and the user. Someone who is naive in the use and is just going through trying needs to know how to do it, but they also need to get feedback. Sometimes that is not easy to observe with the naked eye. You need feedback. I think that is part of the scheduled maintenance loop.

DR. MCCULLEY: Good point, and it also probably should be a part of the initial introduction of the instrument to the site, education of the operators. We can put it under device, that there is appropriate education on the part of the manufacturer to the users relative to appropriate care and maintenance, and that the operator follow those effectively.

Next topic is lamellar keratitis, either focal or

diffuse. Let's see, who came today to tell us what is causing it?

[Laughter]

Okay, device. There are thoughts that interaction of salts with motor head and oils, and the like, are a culprit. So, I am not sure how we put that. That would be relative to the device being developed in such a way that it does not leak and that it is not susceptible to contamination by salts or organisms, and that the maintenance be accomplishable without compromising that principle. That gets back probably to the issue that was brought up before, the question of blades not being contaminated in any way. Are there other things under device on lamellar keratitis? Scott?

DR. MACRAE: Just a comment in terms of this issue. As I watch the literature, initially I think there was a wave of speculation that this was actually device related. As I have seen papers come through the journals, more and more it seems that interface keratitis can't be characterized as always device related. As a matter of fact, most of the time it is not related to the microkeratome, from what we can determine or from what I see in the literature. So, I just want to give that to the agency, that interface keratitis, I believe, is not caused by the device. In fact, we have had cases where we simply lifted the flap,

retreated a patient without using a microkeratome, and we have had interface keratitis.

DR. MCCULLEY: But is it fair to say that from what we know right now that we would have to view this as not a single cause; that it is a heterogeneous etiological problem, and possibly pathways, that the device may have an operator role, and so on and so forth? And that is what we are going to try to do, put the ones that go under each one. But are you proposing that we take device out of potential causes?

DR. MACRAE: No, I am just saying that as guidance to the in-house people --

DR. MCCULLEY: It is not only a device related issue.

DR. MACRAE: -- that it is certainly an important concern, but the literature that I see -- and Dan is shaking his head also -- indicates that the primary cause is probably not the device in most cases.

DR. MCCULLEY: Okay. Point taken. Anything else related to device in lamellar keratitis?

DR. REINSTEIN: I would add that the device may be involved as a bystander because it appears that the literature is leaning towards a theory of endotoxin and it is a sterilization issue. That would explain why instruments could contain endotoxin that were used under the flap under

the same sterilizing conditions. So, the keratome would be involved in the sterilization issue if this is the true story, but nobody has hard evidence for this yet in the literature so it would be hard for us to recommend something because --

DR. MCCULLEY: Well, no, we can recommend something here and we can do it not too specifically but we can say that it would be a device-operator interaction; that if the device is not appropriately maintained it can be contaminated with a stimulating substance, and that we need to ensure that the device is appropriately maintained. Again, would that be an issue here -- maintenance of a device, not contaminating it with other substances; not having our sterilization solutions or apparatuses become contaminated where they possibly can kill the bacteria but leave bacterial products around that could be introduced or carried by the device into the interface. So, avoidance of device contamination with living or dead organisms or other stimulating substances.

DR. MAGUIRE: Is it appropriate for the panel to put in a suggestion that when a cluster of cases occur that we look more specifically at a device? Do we have any role in that? Because certainly there are clusters that have been reported, and with clusters you may be more suspicious.

DR. MCCULLEY: Ralph, you didn't hear that. If

there is a cluster of lamellar keratitis would it be appropriate to charge the FDA with doing a CDC type of analysis to try to determine the causative event in the cluster?

DR. MACRAE: That is not what we are here for.

DR. MCCULLEY: I don't think it is. It would be nice to saddle them with it.

DR. MACRAE: As long as we are on this, I just want to say for the record that I think this would be an ideal area where the Centers for Disease Control would get involved because there are a lot of these cases being observed now and most of us that are out in the field that are seeing them are perplexed, and there doesn't seem to be a lot of systematic evaluation in the way that CDC approaches things, and that is exactly what is needed right now with this problem. I think with that type of systematic evaluation -- this certainly reminds of the acanthamoeba keratitis problem where we had peripheral facts but we didn't really have the bigger picture. I think CDC could be extremely helpful, and I would just like to say for the record that this would be an ideal situation --

DR. MCCULLEY: The reality of the acanthamoeba situation was that CDC had it reported but it was the individuals that figured out the problem more than the agency. That is probably what it will take here unless the

ASCRS -- but we are getting afield. Dr. Rosenthal?

DR. ROSENTHAL: I might just add that if there is a major issue related to something like this Larry Kessler's group that does postmarket, does have an epidemiological group that helps design and carry out studies that might be of interest. That is a potential use of their facilities but, of course, they have all the devices to deal with and they have to have priorities. It depends on what the priorities are.

DR. MCCULLEY: All right, we have gone from a "no" to a "yes" and "maybe."

Okay, operator issues related to lamellar keratitis -- any others? Patient issues?

DR. YAROSS: Back to operator issues, I think someone mentioned the importance of cleaning the equipment and maintenance. So, I think that needs to be under operator.

DR. MCCULLEY: Oh, that was not put in. Thank you for putting that up. It was intended to be put in there. Everybody please try to watch because, again, they have a tough job there and I can do more than one thing but I can't do unlimited numbers and I can't watch that too to be sure that it gets put in. So, all of you, please watch that.

DR. SUGAR: Lid isolation and suction to take away secretions may pay a role.

DR. MCCULLEY: So, operator maintenance of an isolated field, isolated sterile field. Patient issues, any thoughts of patient issues being involved where it is the patient's fault?

DR. MACRAE: This is actually a combination of operator and patient, we have observed a few cases of interface keratitis in patients that have atopic disease, and we think that there is a relationship between the atopism and their inflammatory reaction.

DR. MCCULLEY: Why don't we put under patient, you know, the concern about there being individual patient or type of patient contributory factors, e.g., atopic?

DR. MACRAE: And this gets back to the issue of, you know, we need a good, large case-controlled type series that could evaluate who is at high risk for this and how it occurs.

DR. MCCULLEY: Other comments about lamellar keratitis? Doyle, you don't have anything to add to that? You have a lot of experience.

DR. STULTING: I think everything I would add has already been said.

DR. MCCULLEY: Thank you.

DR. STULTING: I agree that most of the cases are probably not caused by the microkeratome, based on our data.

DR. MCCULLEY: The next item is jagged perimeter,

entry wound, edge, tearing and entry angle. Device is critical here. This gets back to our bevel issue. I guess for a device it would be insurance of an appropriate bevel, a non-traumatic appropriate bevel.

DR. SUGAR: Didn't we really cover this under number three, quality of bed and perimeter?

DR. REINSTEIN: Well, it went up from there actually. The entire box under device could just be copied and pasted in there.

DR. MCCULLEY: All right, do we need to leave this as a separate line, or did we not already cover this under other things? That is not a rhetorical question; that is a real one. Looking back up at the other things, is there anything that we would put here or need to put here that we have not otherwise covered? Scott? Dan? Leo? Anybody?

DR. MAGUIRE: I think it is redundant.

DR. MCCULLEY: Okay, let's X that box.

DR. ROSENTHAL: May I just suggest we put it under poor precision and reproducibility as another line under the second?

DR. MCCULLEY: It goes under bed and perimeter, quality of bed and perimeter.

DR. ROSENTHAL: Okay, quality of bed and perimeter.

DR. MCCULLEY: We have covered it there.

Reproducibility of cut -- we have covered that. Now we come to suction, consistency of, loss of, maintenance or, ischemia of, decentration of flap. Device.

DR. YAROSS: This is one where I think it goes under the possible causes, and we have already picked it up in several other places. There have been several places where we have said you can get decentration, etc., by poor suction control.

DR. MCCULLEY: Okay, well, let's go through them one at a time. Consistency, we have stated that needs to be. We don't want a loss. The only thing we have not covered with loss, and we may get that -- where is our irregular flap? I guess we had that under precision. We did not address, did we, in that the issue with loss of suction, that we need a fail-safe in the machine, that if suction is lost the machine stops cutting.

DR. YAROSS: That is the mitigators.

DR. MCCULLEY: Good point. Maintenance of? Okay. Ischemic globe -- that probably hasn't been covered.

DR. MACRAE: I would make one comment. I think most people around this table would agree that maintenance of intraocular pressure is one of the most important components of this, and that is evidenced by the fact that it shows up again and again in our other subcategories. So for the record, it is extremely important. I think all the

keratome operators also believe that at least in some cases when a machine registers good suction the manufacturer assumes that that suction has been translated to increased intraocular pressure, and we all recognize that there are times when there is a disconnect between the pressure chamber and its connection to the intraocular pressure. That disconnect very frequently leads to trouble.

DR. REINSTEIN: There is that, and there is also the fact that scleral rigidity determines the coupling between vacuum pressure in the system and the intraocular rise in pressure.

DR. MAGUIRE: So that is one component. Another thing for the record that I think is extremely important is accurate measurement of intraocular pressure by the operator. I think some of the methods that we use to do that are difficult for the operator to use, especially someone who is relatively new to some of the applanation devices, and I think -- I don't know how everybody feels, but there should be some discussion about having some kind of a quantitative measurement of intraocular pressure by the operator.

DR. MCCULLEY: Let me get us on track here if I can, or try to. Do we need to add anything anywhere? You brought up some issues. I want to be certain we don't need to add back up somewhere else, and if we do, where they

should go. Consistency -- we talked about establishment and maintenance of. Mitigating factor -- some of the issues you brought up, to ensure that we have it with, for instance, a pneumatometer or a quantitative device would come under mitigation to avoid the problem.

DR. REINSTEIN: Perhaps it should actually be part of the way of doing this, rather than --

DR. MCCULLEY: Well, we don't have a way of doing columns so we have a cause problem --

DR. REINSTEIN: But under device -- what we are talking about is producing adequate intraocular pressure elevation and a stable intraocular pressure.

DR. MCCULLEY: Right.

DR. REINSTEIN: So we need a way of measuring that we have adequate pressure.

DR. MCCULLEY: Right.

DR. REINSTEIN: At the moment the systems that are used are basically using what is called an applanation tonometer which, as Leo suggested, is not easy to use, is quite dependent on how wet the surface is, and it is only a threshold measurement. It only tells you that the pressure is above a certain level.

DR. MCCULLEY: But, wait, wait. That is one of the ways. There are other ways to do it. We have our columns of causes and then we have mitigating factors that we are going

to come back to in a moment. We discussed at length before establishment of and maintenance of adequate suction intraocular pressure. Do we need to embellish on that any more, keeping in mind that we are going to comment on mitigating factors and how to avoid the problems?

So let me start once again keeping that in mind, and keep in mind what we have already discussed and said. Do we need to add anything else to that? Consistency of I think we have discussed. Loss of we have discussed. Maintenance of we have discussed. So all of those relate to decrease in effective suction and increase in intraocular pressure. Ischemic globe, that is too much for too long. That we have not covered.

DR. YAROSS: From a formal standpoint, I think everything except ischemic globe has been addressed elsewhere. The question is, is ischemic globe a separate clinical issue that you need to then identify the causes of.

DR. MCCULLEY: Yes, it is, and an important one. But before we narrow it to that, did we cover -- and you guys help me, looking back up before -- did we have decentration of flap because that is not too much or too little; it is just unusual and relating to other anatomy? I don't think we covered that.

DR. REINSTEIN: Therefore, in that box we should have conjunctival occlusion as a device cause of loss of

suction.

DR. MCCULLEY: No. What I was trying to do -- I am not doing this well because we are not all staying on the same page. We have talked about decrease otherwise in other sections. So, a cause for an inadequate pressure that we have already discussed would be conjunctival occlusion. Would we not address that in mitigating circumstances to ensure that we do not have conjunctival occlusion that, indeed, we do have true suction and true increase in intraocular pressure?

What I am trying to get at is I think we have dealt with the issues that relate to low or loss of suction and high intraocular pressure. We have dealt with that. We have dealt with those. We have two other issues under here. One is too much for too long, resulting in an ischemic globe. The other is some kind of weird anatomical situation or poor surgeon placement of suction that results in decentration of the flap.

DR. REINSTEIN: But nowhere above here does it say conjunctival occlusion.

DR. MCCULLEY: No, because it is going to come under mitigating events and we are not yet to mitigating events.

DR. REINSTEIN: But, for example, having multiple ports for suction would be a device element --

DR. MCCULLEY: And that would be under mitigating events.

DR. REINSTEIN: All right.

DR. MCCULLEY: Unless someone has something different, I think we have dealt with low, inadequate, loss of suction in other areas. We will address them again with mitigating circumstances. Yes?

MR. BARTELL: A factor that might come under suction --

DR. MCCULLEY: Mr. Bartell?

MR. BARTELL: Yes, Mike Bartell -- as you evaluate microkeratomes it would be build up time of suction and it would be suction release as a factor also.

DR. MCCULLEY: And that would probably come under too much or too long kind of circumstance. How would that relate to a problem?

MR. BARTELL: Just not letting loose of the eye when you are there in the OR. You know, it can be a problem. The suction doesn't vent. You know, if you are talking about the subject of suction, if your vacuum buildup time is exceptionally long or the patient's eye moves, that leads to your decentration. In evaluating a microkeratome one of the things I would like to know or would like to see is what the suction buildup time is and what the release time is.

DR. MCCULLEY: Good point. So, now we would go

back under possible causes where we discussed the issue of inadequate suction and have -- well, we can still work that in. Keep the thought. We can work it into mitigating issues rather than redoing the other, and put that there needs to be appropriate buildup and release time. So please hold the thought. You have the responsibility for that.

DR. YAROSS: I think what may do it, if we want to differentiate the clinical issue from the device issue, is that the clinical issue could be undesired IOP and the device issue is suction control.

DR. MCCULLEY: We are tying the two together already. So under suction we are dealing, have dealt with or will deal under mitigating circumstances the low suction. Let's see, it would be excessive -- we may have to break this into two; I am not sure how to put it into one. But it would be suction resulting in too high an intraocular pressure. The clinical event would be ischemic globe phenomenon.

DR. PULIDO: Excuse me, a point of clarification, so a clinical problem is ischemic globe, probable cause for device --

DR. MCCULLEY: Good point, let's do it that way. Thank you, Jose. Well put. So, under the clinical problem put ischemic globe -- just put ischemia, ocular ischemia.

MR. MASTEL: Excuse me, Dr. McCulley, what is

excessive IOP?

DR. MCCULLEY: Too much for too long. It is very individual. It is like defining glaucoma. Okay, so we have ocular ischemia as the event. Cause -- and there is going to be some individual variability that is going to contribute to this so it is probably not a single number, and it is going to take into account both the degree of increase and the duration of the increase, and there is going to be some individual variability. So, I can't tell you an exact, Mr. Mastel, what that would be because there are variables.

But the things that would contribute to the event would be a device that created excessive suction resulting in increase in intraocular pressure. From a device standpoint, it would be a device where the operator cannot accomplish the event in a timely fashion because of design that requires excessive time for the suction. Operator standpoint would be -- I don't know how to put it in a non-pejorative way, but inability to use the machine efficiently and in a short period of time. Patient -- there is then going to be the individual variability of susceptibility to ischemia.

Let me make sure we have all three of these and then we will go on and we can rip it completely apart if we want. That is going to be individual susceptibility to ischemic damage.

DR. ROSENTHAL: I need Dr. Higginbotham's advice, but there is a pressure above which one should never go. I know there is going to be individual variability based on lots of factors but I think there should be something in there that the thing doesn't just put on suction and continue to put on suction. There has got to be a means by which it stops at the level which you have chosen.

DR. MCCULLEY: Dr. Rosenthal, are you aware that we occlude the central retinal artery not uncommonly in this procedure? So, we are shutting off the blood supply to a significant degree. Is there an absolute above --

DR. ROSENTHAL: I don't know; I am asking you.

DR. HIGGINBOTHAM: It doesn't sound like it is really magnitude -- well, the magnitude is excessive but the duration is really the issue here, and certainly my colleague to my left could contribute to this answer but certainly the shorter the better, but no more than, say, a minute to a minute and a half. I mean, the magnitude is 60-80.

DR. MCCULLEY: We have to be careful about that because there is a device approved that requires elevation of intraocular pressure that not uncommonly will exceed a minute to a minute and a half of very high pressure.

DR. HIGGINBOTHAM: So now we are getting really into the entire retina in terms of good circulation and what