DR. STRONG: I think I can help answer that. Again it's Strong in Seattle.

I have visited many of these countries, and most of the standards that have been developed have come from AATB, because the original standards were developed in AATB. So they have followed along.

So I think, if anything, the other countries, including the European Association of Tissue Banks, the Asian Pacific Association, have followed AATB standards, but they are probably even slightly behind our own, although I must say that in Asia, for example, because they have such difficulty with donors for cultural and other reasons, that the majority of their tissue is irradiation sterilized.

So one could question which is the safer way to go, but they do use the high dose sterilization in those countries.

DR. SIMON: I believe -- I'm not an expert on this, but I believe the organ procurement is separately regulated through other Federal statutes and, I guess, not by FDA but UNOS is under some other part.

DR. SOLOMON: Yes. That's correct. HRSA, Health Services and Resources Administration, regulates organ transplantation. FDA does cells and

tissues.

In terms of whether autologous tissue is removed and then put back into the same individual, we have that as an exemption from registration. So that is not regulated by FDA. The hospital JCAHO probably has standards, but that was an exemption in our registration rule.

DR. SIMON: I was going to say, you know, there's a little bit of sort of de javu or interest as a blood banker sitting in on this discussion, because when the public became concerned that blood was transmitting infection, there certainly was a regulatory response from FDA who had some very strict regulation.

I guess the FDA clearly knows how to do it. If there's a sense that the voluntary regulation through the tissue banks is not adequate and that the current state of regulation is not adequate, then I think the same rulemaking process, regulatory process, that was used, that has been used in blood banks, could be used here.

If there's a sense that this is a very rare breakdown in the system and this is not an ongoing problem, then perhaps one needn't go in that direction, but it seems to me that that's where we are

here.

CHAIRMAN NELSON: Okay. In order to try to meet our deadline, I would like to move to Dr. Eastlund who is from the University of Minnesota for the next.

DR. EASTLUND: Good afternoon. My name is Ted Eastlund. I am the Blood Bank Medical Director at the University of Minnesota, and I'm happy to come here to give you some words representing the American Association of Tissue Banks of which I've been a President in the past.

Some of my early remarks can't always be attributed to AATB, though, because at the end we will make sure we'll discuss that for five minutes or so, but I will try to take an equal amount of time to give you some background on cadaver tissue donation, use, complications of it, and what is done to prevent that, and then go to the issue of the recent reports since November of infections from allografts. I -- Well, that's enough about me.

The American Association of Tissue Banks has been in existence since 1976, and it is a voluntary, as you know, professional organization similar to the American Association of Blood Banks. It has approximately 1200 members, and there's about

74 tissue banks involved.

It is there to establish standards. It also is there to inspect and accredit, and it also certifies tissue banks. So hundreds of tissue bank specialists that are certified are operating in tissue banks in the United States.

To start -- next slide. And you should have a handout also that has all of these slides. So we will go quickly this first five minutes or so.

I've listed in here from a while back a multiple of tissues that are used routinely in the United States, and many of them are structural, the ones on your right on your handout and up here -- or your left up here, I should say. The others are more metabolic and for replication and, of course, blood fits into that area. Next slide.

But in tissue banking, most commonly it's thought of as these types of tissues, not exclusively but bone with hundreds of thousands of bone components, products being used every single year; corneas with who knows exactly, 40-50,000 corneas transplanted a year, or so; skin; tendons; cartilage; and heart valves. Next slide.

Because this recent exposure of risks for bacterial infection came up with tendons and bone, I

thought I would just say a few things about that. Bone banking, bone transplantation was done by pioneers for close to 50 years, and it really usually meant large pieces of bone, unprocessed, which are shown right here with a person with a not so malignant giant cells tumor of the distal femur, and a chunk of donated bone was implanted over there to the right. Next slide.

Equally so, up on the top of the humerus up here, an equal mount of bone was put there to replace to replace the cancer. And indeed it works, and it was successful, and this type of tissue with bone banking went on. You might say it was not large scale bone banking, but it went on for quite a while.

When cyclosporin came around to suddenly make organ transplantation very useful and common, it led to the required request legislation in 1987, and suddenly there was an explosion of available donations, and cadaver tissue donation became a very large availability. Next slide.

With it, and even before, came another very common use of bone, and that is to revise those hip implants who became loose, a fair percentage, after 20 years. For instance, it might protrude into the pelvic cavity or it might migrate upwards. Next

slide.

You could use a piece of bone, commonly even in one way as a femoral head, and shape it, screw it in, and use it. Next slide. Or if it was erosion of the proximal femur for loosening, then you could take a section of cadaveric proximal femur and place it into that site. Next slide.

In the November and in the December MMWR articles, it was prominent about sort of living, fresh osteochondral allograft, the Minnesota case, and also in December came four patients from two tissue banks where patellar tendon for anterior cruciate ligament repair were associated with infections in recipients, and it's those cases that led to notification to AATB to start becoming active and involved in evaluating these and look for preventive measures and look at existing standards and practices.

So this is the anterior cruciate ligament that can be repaired. Next slide. With it, you can see on the top a bone tendon block. The bone is a little butty on each end, but that's part of the patellar bone, the patellar tendon of a cadaver, and also the proximal tibia piece of bone. Next slide.

It shows you that you can screw into place the bone on the proximal and the distal part of the

knee and have an equivalent of a new ACL. Next slide.

This is the bone screws that can hold in the bone, and in these cases bone screws are involved also. Next slide.

Now go to the different kinds of infections that can be and have been, I should say, clearly transmitted -- clearly transmitted from bone graft. Not a question of association with, but were documented cases in the literature.

We can't go over all the viruses and other proteins that can infect, but you can see bacteria. All the way across the top is the number one or most common thing that -- not in numbers -- but it's there for all those tissues. Next slide.

In bone we have known for years that Hepatitis, HIV, tuberculosis and bacteria has been transmitted in the past. Next slide.

Matter of fact, the oldest case, in the Fifties, was actually tuberculosis where, you know, you used to collapse the lung, plombage, put in things, take the ribs, and you can use them in other patients and transmit tuberculosis into spine, surgical recipients. Next slide.

But when you look at sort of prevalence of how common is it, some of the pioneers, Mankin and

Tomford and many others, these surgeons here even are involved with that organization, the early bone banks. They looked and they found around out of 300 recipients had a bacterial infection that they thought possibly was related, but when you looked at clinically, you didn't see there was any clearcut evidence that these were really causing the infection, except on the bottom one where three recipients had *Serratia*, and indeed it was from the same donor.

So there was some indirect evidence that it could have been the bone after all, but it kind of represents what I have sort of learned over the years, that if it is caused by an allograft, it's very, very rare and even probably rarer than this. Next slide.

Then a few years ago it showed that processing can actually introduce things to cause allografts to cause infections, and in this case it was actually a pericardium used as an equivalent to dura to replace a dural defect in the craniotomy surgery.

In this case you see they had balanced salt solution, which is an *in vitro* reagent used to wash the pericardium. That had anthropi -- *Ochrobactrum anthropi*, and also three recipients developed the same in their meningitis infections.

So processing in this case an equivalent. Three years before that it was shown in processing a pancreatic islet cells infected plenty of patients with *Enterobacter cloacae*. So processing itself can also contribute. Next slide.

What do we do to prevent this? Just like blood donations, just like organ donation, any of the transplantation, it's donor health screening, physical exam, blood tests, autopsy if it's a cadaveric donor, and tissue processing steps. Next slide.

Medical history is similar. First of all, for blood donors you asked the same questions, but you ask a lot more, because not only are you trying to reduce transmissible infection and malignancy, but you can have conditions that can make the tissues unfit for use. So all those things are looked for, and then the universal same questions for HIV and Hepatitis behaviorals. Next slide.

The testing that is required by AATB is HIV antibodies, Hepatitis B surface antigen, HTLV, syphilis and HCV. Of these, HIV and Hepatitis B surface antigen, I think, have FDA approved kit with caveric blood. Next slide.

Physical exam: It's a little bit more than a blood donor, but we indeed look for injectable

drug sites, but also behaviors of HIV infection and also trauma over donated sites or sites of infection in the patient physically also. Next slide.

So in general, it's the same. But the most important things to reduce the risk are the fact that it is voluntary, the fact that medical history screening takes place first before you do testing to avoid an unnecessary high rate of false negatives, and then there's donor procurement and testing. Next slide.

The processing is alluded to already. First of all, the collection: It's done in a morgue or in a surgical suite, very commonly with prescribed methods for cleaning and preparing the room, cleaning and preparing the body, sterile drapes, sterile equipment, aseptic surgical procedures, preserving blood vessels for the embalmer, and also bacteriologic testing is frequent. Next slide.

At processing, which is already alluded to, the clean rooms that are used are similar to medical device type clean rooms, controlled environment, debriding and cutting into the desired shapes, disinfection steps, sterility testing, final packaging and, for many tissues, final sterilization steps. Next slide.

Now what came up again since December were these cases; first of all, the Minnesota case of a death. We won't go over that. Next slide.

Then two other cases, two other tissue banks, a Florida tissue bank and a Texas tissue bank in the December MMWR by the CDC. In one, which I will call one case, but it was two patients, they had infected ACLs. These were not *Clostridiums* but *Klebsiella* and *Citrobacter*, and also they found the same organisms on the bone at the processing tissue banks.

What happened here was the final release procedures were inadequate. They thought everything was done, but it really wasn't irradiated, even though they said it was and distributed it. So it was a mistake, an error of release. That's what caused this whole thing. Next slide.

Whereas, on the other one it was the case of two patients who had *Pseudomonas aeruginosa* during ACL repair, arthroscopically putting in a patellar tendon implant. Both patients three weeks later developed a serious *Pseudomonas aeruginosa* infection. It was in the same surgical center, different arthroscopes, different surgeons, different days of surgery, but it was from the same donor. Not only

that, but it was from the same left knee.

Now -- next slide -- but since this was an AATB accredited tissue bank and it was the only one we knew at that time that was AATB accredited, we inspected them. Two inspectors thoroughly inspected it and could not find any evidence that it really was the donors that were involved.

These other findings which looked like enough to say it was from the tissue actually might be circumstantial, because when we looked at it -- I won't take time to go over all the details, but there were no signs on the physical exam type or blood testing during processing.

This was in a clean room, Class 100 with Class 100 area for the critical processing, and in a larger Class 1000 procedure. The testing that was done: First of all, monitoring of clean room during that time period was totally normal. No *Pseudomonas*.

Then when it was irradiated, it was done in the normal fashion. When it comes back, you look at certain things to see was it truly irradiated, and I've listed those things.

The spore strips that were put in there that are infectious -- they were no longer -- there was no growth. The cold process, companion pieces

from the same tissue that was processed and came back with no growth.

The digital indicator, sort of like an irradiation visual indicator only these change color at 1.5 million rads, not 2500 in blood -- they changed color. Dosimetry -- that is, testing to see what dose was actually applied at the irradiation facility -- that demonstrated it was 1.6 to 2.0 megarads, and other tissues from other donors in the same box all came back no growth.

So we looked at it as saying, okay, this was irradiated. There's not any question about that. And yet everything points to this donor. Next slide.

So we came to the conclusion that we cannot tell you what happened at this accredited tissue bank or what happened in the recipient to cause the *Pseudomonas* infections in two patients at the same place.

It could have been the tissues, but we found no evidence. We found evidence that it probably wasn't, but you can never say for sure. Matter of fact, what puts a question in your mind: If you look at the D_{10} value for *Pseudomonas aeruginosa*, the D_{10} value is the dose of irradiation that will eliminate 90 percent of the bugs.

Well, this has a very tiny one, and these numbers will show you that it reduces 300 logs of bacteria, even with 1 megarad, and make a 1.6 to 2.0. Next slide.

Just as another illustration that other things can have an impact at the surgical site, and I'm sure this was looked at, but even last week they showed that some bronchoscopes can transmit *Pseudomonas aeruginosa* because of some loose ports, and that was at Johns Hopkins. Next slide.

Last, I'll just go over old information that shows, even taking clean sterile packs of supplies and a sterile clamp and putting it into media, you can have up to 2.7 percent on average in multiple sites of contamination and bacteria. So you all know that OR sites can also contribute to this. Next slide.

So in summary, we have reacted to the two cases -- that is, two tissue banks, the MNWRs and working with the CDC in December where one of the patellar tendon cases in two patients was clearly from tissue bank error, but the other one -- oh, and then the other one that we looked at, we could not figure it out. So basically, we were left with the Tissue Bank A one where there was a failure of inadequate

control of bacterial contamination.

They have been the cause of focus of attention on these things by our organization: Microbial control during allograft processing; final release procedures; the existing state of reporting and investigation of infections; and also the lack of a need for studies on the prevalence of infections in these patients. Next slide.

What we've done since then is form a special task force of which I've been the Chair, and we inspected the tissue bank involved, and it looks like we have some more to look at, and we have reviewed our own standards and actually made some changes in that already regarding procurement cultures.

We are going to be working developing guidance documents and taking some of the ones that were mentioned in our technical manuals regarding bacteriostasis, regarding culture requirements and sampling requirements at the -- and look at those to see which ones require more standard setting versus voluntary guidance.

At our workshops next week at the mid-year meeting and our annual meeting, we will be covering in detail with CDC and others infectious complications,

types and prevalence standards, regulations, sterilization steps, disinfection steps, and the bacteriologic testing. Next slide.

So a final comment is that we really are thankful that we have been working with the CDC and actually look forward to further working with them and collaborating in both investigations, also in prevalence studies and in preventive steps, and in general we have been in agreement with them about the steps they recommended to Tissue Bank A.

Most of these recommendations have already been in our standards or manuals already.

Thank you. Any questions?

CHAIRMAN NELSON: Thank you. You know, in contrast to the *Clostridium*, the *Pseudomonas* is a ubiquitous aquatic organism. Was there any storage or exposure to aqueous solutions or anything like that in these cases, you know, after they left the tissue bank?

DR. EASTLUND: Well, during processing, of course, it's used with on-site manufactured sterile deionized water. That had -- We looked at the records. All the quality control testing and the routines were all normal, and nothing there; whereas, implantation -- that's a different question.

I'm sure there was plenty of flushing and irrigation, but that's at the time of surgery inside the joint, and not necessarily storage.

DR. DOPPELT: Well, I just wanted to make a few comments. In one of the -- You mentioned the bronchoscopy and the *Pseudomonas* there. For those of you who don't know how arthroscopic procedures work, usually the equipment is sterilized the day before and, if you are doing multiple procedures, the first cases that you do, because you have like two or three scopes in the hospital -- the first set, the first couple of cases are done with what was already sterilized the night before, ethylene oxide.

Now there's newer methods with ionization. When you are getting to your third or fourth case, the equipment may be just placed in some bacteriocidal solutions. So it isn't really as sterile and clean as if it had been sterilized the night before.

For those of us, for example, who do arthroscopy on patients who have already had allografts or who have total joints, like a total knee, we insist that those cases be done as a first case so that we know that the equipment has been properly sterilized.

So in this particular instance, we have

tissue coming from one bank, two pieces of tissue, that the recipients ultimately got *Pseudomonas*. If I understand what Dr. Eastlund is saying, and I believe I agree, that I don't see how that tissue could have left the bank with *Pseudomonas* being on it.

I mean, you have to eliminate what's impossible, and anything else, no matter how unlikely, is possible. You know, the log order for sterilization was -- I mean, just there could not be *Pseudomonas* on that tissue. So it has to have occurred someplace later.

Then I just wanted to add one comment that Dr. Simon -- in response to Dr. Simon. The AATB does have standards, and the FDA has regulations in terms of procedures for processing. In 1996 we had required in our standards that you shall, must, get pre-processing cultures.

There was perhaps some overconfidence that the final cultures and the processing of decontamination and washing and so forth would eliminate virtually everything and that it would be appropriate to change that to "you should" obtain pre-processing cultures, but you still have to get final cultures.

Now Dr. Kainer has pointed out that there

are, obviously, some faults with that, because of issues of bacteriostasis. We have since gone back and had the Task Force on Sentinel Events and the Standards Committee review all of this, and it was their recommendation, and the Board approved it, to go back and insist that all banks, all accredited banks, have pre-processing cultures.

Nevertheless, the AATB had done a review of the banks that were accredited, and they had reviewed 50. 45 or 46 out of the 50 still continued all these years -- I mean since '96 -- still continued to do pre-processing cultures. So the majority of tissue that was processed and distributed had always had pre-processing cultures.

So we have tightened things up, but that has been the case, that the pre-processing cultures for the most part have been done and will be done.

DR. SIMON: The question I would like to address, which is a continuation of my prior comment, of course, to Dr. Eastlund, our speaker and perhaps also to Dr. Doppelt: Given the outstanding job that it appears that the AATB is doing with its member banks, but assuming that it's not a legal requirement to be a part of that, do you feel that the FDA needs to create a regulatory process, environment, paradigm

that is more similar to what it does for blood?

DR. EASTLUND: Well, first of all, the FDA has good tissue bank practices in the -- ongoing, not yet finally implemented, and has a number of things there, and they have the inspection capacity already. So I'm not the one to ask, but I'm not sure -- I think it's sitting there.

DR. SIMON: Well, you know, yeah, I would agree, it's sitting there. The question is does more need to be done with it, because, for example, we heard a lot about, well, you know, we can't get people to report this. Well, among the blood banks, you know that the FDA has ways of making sure that we do what they expect us to do, and it's been a very firm regulatory process.

I guess the question is: Is that needed here or is that not the case or is it adequate? You seem to be saying you think it's adequate.

DR. EASTLUND: Well, in many areas -- I mean, for instance -- I can't answer the resources of the FDA, but reporting requirements -- that's still an open issue, because tissue banking sit right in the middle of a couple of monolithic establishments.

One of them is blood banks who are responsible for the traceability in a hospital for the

blood. You call ten years later from a blood center, and you can find out the recipient. If you are a recipient, you can call ten years later and find out who the donor was.

So tissue banking is not quite like that. On the other hand is the medical device manufacturers who are responsible for tracking, and they have the patients -- or the orthopedic surgeons filling out a form that goes to the manufacturer who is responsible.

So tissue banks are in between. Is it the tissue bank, manufacturer, responsible or is it the hospital that's really responsible to keep this flow going?

We are in between, but in the early Nineties the American Association of Tissue Banks went to JCHO to try to get their agreement on setting up standards so that hospitals were responsible for logging in, for proper monitoring and storage, and for keeping track of the recipients.

We also went to AABB who also has a standard in the area of what's called tissue dispensing facilities that requires, again on a voluntary basis, that the facility that uses the tissue, that has gotten it from an outside supplier, is responsible for this traceability.

So it's there, but how it sits with requirements for the FDA to hear about it is another story. I don't think at this point, although the new emergency regulation, I guess, implies some of that maybe about mandatory reporting of deaths.

Currently, you may get very good actions by a tissue bank if they get a report of a positive culture and they investigate it and find out it was nothing that was related to the tissue, they will send back -- they will do a root cause analysis and stuff, and send back a letter to the surgeon in the hospital. But it ends there.

If they find a true infection from their tissue, then they still report it to the hospital, but they don't necessarily report it to AATB or FDA. So I'm not sure where that sits as far as the requirement to report to FDA a transmitted disease by the tissue.

DR. SOLOMON: Could I just clarify? The way FDA regulates blood and the way FDA regulates tissues is quite different. Blood components are licensed products. They have been regulated since the Seventies or maybe even earlier.

I don't know if Linda could talk to that -- Dr. Smallwood. But anyway, they are regulated both under the PHS Act, which gives us the authority to

require that they be licensed, and also under the FD&C Act, which gives tremendous authority in terms of GMPs and other things that you find us doing to blood banks.

Also for blood components, in order for a blood bank to get a license it has to submit an application to FDA, and the application is reviewed in terms of the SOPs, and various QC data have to be submitted, and then FDA grants that blood bank a license. So we have quite a bit more regulatory tools when it comes to blood banks.

Now tissue has only been regulated since '93, and a conscious effort was made then not to be over-heavy handed. So that the authority under which we regulate tissues comes just from the PHS Act, and it's Section 361 which speaks to communicable disease.

In other words, tissue banks are not licensed. Tissue banks do not have to submit an application with any data and get approved. Tissue banks do not have to follow GMPs.

As I mentioned before, we are trying to get GTPs in place, but they are not effective yet. So there's quite a difference in the degree of regulation and the legal authority behind the regulation.

DR. HARVATH: I was wondering, for the

AATB's experience the thoroughness to which the history of your donors, your cadaveric donors -- what kind of compliance do you get with your tissue banks? I mean, if there's a piece of missing information, for example, someone who may not have an extensive medical history file -- If there is a piece of missing information, does that disqualify the tissue from being harvested?

DR. EASTLUND: Well, there is a whole list of required information that must be -- just like a blood donor's history. There's always more information out there that you could always get also.

For those required -- Another difference is that required information comes from the next of kin. So you can always say, well, this is not a direct interview of the donor. So there is that issue.

There is also the same issue as there is in blood donors of more information out there you could go after if you wanted to. Now if it's an autopsy that is done, we need to look at that, and it does not require that there is an autopsy.

On the blood side, if a person had Hepatitis five years ago and was reported to the State Department of Health, the blood bank won't know that

necessarily. I mean, so there is always more information you could have.

The basic required information must be obtained or you do not use that donation. You do not make the collection, period. So there is a prescribed amount that must be there, period. You can just say that the sources maybe are different than a living donor.

DR. HARVATH: In your experience as an AATB inspector site visitor, do you find that there is absolute compliance with those requirements?

DR. EASTLUND: For many years, there's been very compliance. Otherwise, they wouldn't be accredited. Not all banks are accredited tissue banks, but that's an absolute. You don't get accredited unless you do it, period.

DR. FINLAYSON: I hesitate to try and add anything to Dr. Solomon's magnificent description of tissue, but inasmuch as this is the Blood Products Advisory Committee, I wanted to add one small historical fact on blood regulation.

I believe the Public Health Service Act, as it was amended in 1944, mentioned blood, and I believe that the first blood bank was licensed in the mid-1940s. Actually, there were blood products which

were licensed even earlier than that. Albumin, for example, was first licensed in 1941, immune globulin in 1943, and blood grouping and typing agents at the same time.

So it's not since the Seventies. It's more like the Forties.

DR. STYLES: I don't know if anyone else was -- or maybe I'm just naive, but I was rather struck by the lack of oversight by the FDA in this area. I would have thought that anytime you -- I mean, look at all the oversight in xenotransplantation from animals, and yet, gosh, when I read through this, I was like you mean they are not already requiring this?

I mean, I don't know that I speak to the issue here, but I don't know if anyone else was a bit stunned by that.

DR. HARVATH: I can only speak to it as my experience when I worked at FDA, but just in the area of hematopoietic stem cell transplantation, you know, FDA has not regulated that, you know. So I mean this whole proposed approach to cell and tissue based therapies was really an attempt to become more inclusive of these areas, and there's been enormous amounts of work throughout the 1990s, especially from

1995 on, in trying to capture this information and try to work with the different communities involved in these areas of cells and tissues.

Some of the areas have been very cooperative in working with the agency, and others have been quite skeptical of FDA becoming involved in regulating that area.

DR. STYLES: I will say that I was struck that it seems like the organization has been very forthcoming and seems to be, at least from appearances, very cooperative with the overall process, which I think will probably, you know, mean that people won't come down on you when you cooperate. But I just wanted to point out I was just amazed by that. I didn't even know that about it. I thought they were all -- I thought it was a blood product.

DR. LINDEN: On that issue I have a little bit of perspective about regulation of tissue banks. We in New York have been regulating them since about 1989, and there has been great improvement.

I mean, my major comment would be this is a slow process. You can't adopt a regulation and expect everybody is going to just comply overnight. When you set standards, it may take a couple of visits before people really fully understand what is expected

of them.

It's not like the blood bankers who are very compliant, really understand the expectations. Additionally, with tissue banks there are a lot of other challenges. As was mentioned, you are not getting the history directly from the donor. Things are technically more difficult.

Most of the -- Many of the facilities are for profit, and not that there is anything wrong with that, but that there are proprietary and competitive issues that we don't see as much in blood banking. But there have been great improvements, and I think that FDA really has the right idea of adding to their existing regulatory structure with the Good Tissue Practices.

That will be a big improvement, but we all have to understand that's going to be a slow process that will take some time. But I think we are really making steps in the right direction.

DR. LEW: This may have been mentioned earlier, but how many are really involved with the AATB group, and how many tissue banks are totally separate, and does FDA's rule, I'm assuming, is for everybody, not just those involved with this organization?

DR. SOLOMON: That is correct. You have to follow FDA regulations whether you are accredited by AATB or EBAA or not. It has no relationship.

DR. LEW: So what percentage are a part of this AATB group, and what percentage aren't, and is it public information to know when you do your inspections? Is there a difference in terms of which one violates these rules more often?

DR. SOLOMON: I wish we had someone from Compliance to answer that. I can tell you that, in terms of prioritizing the inspections, if a bank is AATB or EBAA accredited, that would be a lower priority in terms of FDA visiting them than a bank that was not accredited.

I don't really know the numbers. I think it's about 60 percent of the tissue banks are accredited. I don't really know.

DR. EASTLUND: Well, I'm not sure either. I think Sam could help, but I have heard someone say that over 90 percent of the tissues used is from accredited tissue banks. That is, bone tissues.

The other question is what percent of the infections were from accredited tissue banks. There's two different questions. It looks like, from your data, there are -- Of course, the bulk of the

Clostridium ones were from a nonaccredited bank, and the other bacteria are still ongoing investigations, including a couple of AATB accredited banks.

So I'm not sure of the answer. Sam, do you have an idea about the percentage of nationwide use of bone type tissue?

DR. DOPPELT: Yes. I think -- Well, I don't have an exact figure, but for bone, as I said before, there's about -- Overall, considering bone, skin banks, etcetera, there's about 73 or 75 accredited banks.

For those that are doing musculoskeletal tissue, the accredited banks account for, I think, somewhere about 95 to 98 percent of the tissue that is distributed in the United States. Now the other two to five percent -- there could still be a fair number of smaller banks. I mean, you only know what you know, and you don't know what you don't know.

So I'm not sure how many other banks there are. Membership in the AATB is a voluntary sort of thing. So we don't have any way of forcing people to join or follow the standards, and I think the proposed GTPs will go a long way to sort of getting everybody on the same page.

DR. EASTLUND: One point about that, if I

could just say that the -- to remind you that the bulk of the tissue transplantation is bone, and the bulk of these infections have been osteochondral and tendons with just a little bit of bone.

So I think it would point to a general good track record of most of the bone transplantation that's going on.

DR. HOLLINGER: Obviously, I think that tissue banks should be accredited. They all should be accredited by some organization, whether it's the FDA and/or -- sounds like the AATB. Sounds like they are doing a very good job of regulation or at least looking at their banks.

A question I had was, if you can tell me, among the AATB banks what percentage of the tissue banks -- or what percentage of the tissues that are obtained are from the medical examiner's office, and is there any difference between the cultures which are pre-processed cultures and after the processing? Is there a difference in the amount and number of the tissues, the percentage of tissues that are destroyed because they are contaminated?

DR. EASTLUND: I'll sort of rephrase the question, too. I think you are asking what percent of all the bone type tissue collected is from a morgue,

whether it's a medical examiner or not, versus an operating room.

That percentage has changed over the years where it used to be bulk of it non-OR ten, 12 years ago, to the bulk of it being OR or a thing that's even more controlled, a collection facility produced and -- put in by the tissue bank, and that sometimes is in a medical examiner's office, a dedicated room.

So now it's changed over to most of the tissue is in a very controlled atmosphere, not the morgue. And the morgue ones are done with a prescribed amount of cleaning ahead of time. But for numbers, I'm not sure if Jean or Bob or if Sam has a number.

DR. SCHMIDT: If you are saying, Ted, OR, this means living donors?

DR. EASTLUND: No. This is a -- The routine is that, once someone dies, they may have a temporary storage in the morgue, and they are brought up into the OR. That's absolute routine.

DR. SCHMIDT: We've just really talked about cadavers today, but aren't there bones from living people and other parts?

DR. EASTLUND: That's right. The most common is the femoral head, which I alluded to. Well,

I think I did -- the femoral heads from total hip replacement. That has died off quite a bit, because there's such a large need for bone, and that can provide a small amount.

So the amount of living donor bone has declined, but it's still there, to a degree. And that is under the same standards. It's a little different, though, because since you are a living donor, you can be retested, and that's a requirement six months later to be retested. And they also get hepatitis B core testing, at least in our standards in accredited ones, and retesting for HIV and HCV at the end of six months.

That was a long history, but that was set in place because semen transmissions back in '85 in Australia, and that's a routine for all of our semen banks also, the same retesting plans.

DR. DOPPELT: I was just going to just sort of reemphasize one point, so there isn't any confusion. I think very few procurements now are done in morgues. I don't know -- I don't have a figure, but clearly, as Dr. Eastlund said, the numbers have shifted.

So when an individual is pronounced dead in a hospital and they are a suitable donor, the

procurement occurs in that hospital, usually in that hospital operating room.

DR. HOLLINGER: We're going to talk about this in a minute, but I'm not sure that's true for corneas.

DR. DOPPELT: You're right. That's a different --

DR. DiMICHELE: I just wanted to ask Dr. Eastlund a couple of questions.

With respect to -- You said donors are voluntary. That means that the people who are determined to be suitable donors are people who have already signed a little card that I'm willing to be a tissue donor. Is that what you mean?

DR. EASTLUND: No. I was alluding to paid versus nonpaid donors, whereas in blood it's definitely a high risk to pay the donors. It increases risk of infections. Whereas, in cadaver tissue donor they are not paid.

It's not that they have agreed ahead of time, and even though they have signed a donor card --

CHAIRMAN NELSON: What would they do with the money?

DR. EASTLUND: Well, as you may know, this is a hot issue in transplantation, because of the

shortage of organs. Right now, it's very much on the cusp of giving money to the next of kin to help with funeral expenses as a motivation or as a way to increase the number of organ donors.

In tissue donors there is no payment.

DR. DiMICHELE: Well, then I have more questions, because the question is, okay, so who is determining the suitability of the donor then, and -- Okay, let me ask that question first, because I have a follow-up.

DR. EASTLUND: The tissue bank staff directly interviews the next of kin.

DR. DiMICHELE: Of everyone who dies?

DR. EASTLUND: That's right. When it's a donor, a potential donor who dies, there is immediate screening. A small percentage of those who are approached actually meet the suitability requirements.

DR. DiMICHELE: And with respect to that, one of the things that you said is in terms of the history. You said that conditions -- you know, that you check for conditions rendering tissues unfit.

Now I don't expect you to go through the whole list of those, but are there a lot of conditions or just a few conditions?

DR. EASTLUND: There's a lot, and it's

specific. If you have rheumatoid arthritis and everything else is okay, you don't donate bone.

DR. DiMICHELE: So it's pretty stringent?

DR. EASTLUND: It is stringent.

DR. DiMICHELE: And lastly, you know, the kind of regulation, again coming from the blood industry, whatever, that we're kind of used to requiring the FDA is very labor intensive, is very financially intensive in terms of the resources that are required to police the operations.

How does your organization fund itself in terms of policing the -- or inspecting and ensuring a certain quality of your member organizations?

DR. EASTLUND: American Association of Tissue Banks, you mean?

DR. DiMICHELE: Yes.

DR. EASTLUND: Well, it has, of course, dues, and that can be fairly expensive, but a large portion is also annual meeting income. To give you an example of American Society of Hematology, they recently reported in their annual report, 40 percent of their revenue was from their annual meeting, and that's -- I'm sure for AABB it's another big bulk of the whole revenue.

There is also fees, if you are accredited

for inspection. So it's more fees for a tissue bank than it is for an individual person. So it's a member organization of professionals plus, you might say, an establishment organization of tissue banks, and there's different fee schedules for them.

DR. DiMICHELE: And how many people work through the AATB?

DR. EASTLUND: Only about 1,200 members and about 74 tissue banks or tissue establishments?

DR. DiMICHELE; No. How many people are doing inspections?

DR. EASTLUND: Oh. Well, we have --

DR. DiMICHELE: Full time staff, I mean.

DR. EASTLUND: Two or three full time or near full time tissue bank inspectors. But there is also voluntary inspectors that accompany them. So you have the professionals in tissue banks with inspectors also. Not so much voluntary anymore? Okay. So they are all paid inspectors, and it's the staff that do that.

In our inspection of these problems that develop, we've had one voluntary professional plus a paid professional.

CHAIRMAN NELSON: Could we get your name for the record?

DR. EASTLUND: Jean Moew, Executive Director of the American Association of Tissue Banks.

MS. MOEW: Were you referring to the size of the staff or the inspectors?

DR. DiMICHELE: I was referring actually -- Yes, to the size of the staff and, you know, inspectors. Who carries out this function, I guess?

MS. MOEW: Okay. We have seven people on staff, and we have three consultant inspectors, and that's the size of the staff. We develop standards, inspect and accredit the bank, and certify personnel who work in the bank. It is a lot of work.

DR. DOPPELT: I might just add one point. As De. Eastlund mentioned, there is a fee associated with being inspected. So, you know, the AATB doesn't send these people out just for nothing, but that may be one -- I'm not sure, but that may be one reason why some banks that aren't accredited choose not to be, because they don't want to pay an inspection fee. They may or may not be able to pass muster when they get inspected, but there is a cost associated with being inspected.

MS. MOEW: Oh, and I meant to say that the people who do our inspections are all, except for one, former FDA inspectors, and one of them is a former

head of CBER Compliance. So we have, we feel, a very professional group doing our inspections.

DR. ALLEN: Two questions. Health care economics being what they are today, I assume that hospitals charge for the use of the operating room for harvesting of tissues, and I just wondered who actually pays that? Is that the collection organization that would pay that?

DR. EASTLUND: Yes. Number one, there are no expenses that the donor family is responsible for. Number two is there are some places that do not charge for that. But number three is that the procurement facility -- the procurement agency then has to pay that.

DR. ALLEN: Okay. And second, what is the background and training of the people who harvest the tissue?

DR. EASTLUND: The qualifications of the people who do the actual procurements vary quite a bit. We happen to have over the years a mechanism of certifying procurement specialists and tissue bankers.

So within the AATB accredited banks, they have a course that is taking place and a certifying exam, and it's quite comprehensive. Then, of course, there is on-the-job training.

As far as qualifications for education ahead of time, it's widely variable, depending on the tissue bank; whereas, some might be medically trained in the beginning, there are some that are funeral directors. We have physicians that do it, nurses, medical technicians. It's a wide variety. Dental assistants have been procurement specialists also, but you have to go through the training first.

CHAIRMAN NELSON: I'd like to move --Yes?

DR. LEW: Yes, just one other thing. It sounds like you all are very good about going to different places and inspecting. But I'm just trying to think in terms of what FDA has suggested, to gather more information, and particularly to look at the issue of infection.

Is it available to you, particularly from your member people who belong to your organization, to get data like on the percentage who have positive cultures, what grew, and then after they are put in a special antimicrobial solution, you know, how often do they have to do that to sterilize it, and what do you allow? Are there standards where, you know, after you have tried once or twice to sterilize and it doesn't work, then you have to get rid of it?

Is all that information easy for you to

gather to offer to FDA for review?

DR. EASTLUND: It's obtainable, and currently the CDC is working with the AATB for a very detailed look at that.

CHAIRMAN NELSON: Okay. In order to try to finish up, I would like to invite Dr. Michael Lemp to talk about adverse reactions after corneal transplants, the eye banks perspective.

DR. LEMP: Thank you very much, Dr. Nelson. It's a pleasure to be here this afternoon.

What I'd like to do in the time that we have here is to go through quickly some of the slide material which you have all been provided, and share with you some of our experience in eye banking.

I am Clinical Professor of Ophthalmology at Georgetown and George Washington University. I'm a corneal surgeon. I'm a former member of the EBAA board, and I've performed about 3,000 corneal transplants over the last 30 years, both here and abroad.

What I'd like to do is share with you a little bit of our experience in eye banking, which I think might be germane to some of the interests that you have here, because we have a fairly extensive experience going back approximately 50 years in this

subject. Next slide, please.

The first eye bank opened in 1944 in New York City. Corneal transplantation actually has a history that goes back about 100 years, but it's really only been done in any large numbers for about 50 years. So it was really in the 1930s and Forties a rare operation.

We had no system of getting tissue. It was catch as catch can when donor material became available. It was only in the 1950s that corneal transplantation developed to the point where it became more widely used, and particularly in the 1960s.

This is why that you find that the EBAA was founded in the early 1960s. It's the oldest association of transplant organizations. It went through a series of developments. So that by 1980 medical standards were promulgated.

There are 93 member U.S. eye banks. There is only one eye bank which is not a member of the EBAA in the U.S. So it's a pretty inclusive organization. In .the year 2000, 46,000 corneal tissues were collected by members of the EBAA. About 35-37,000 of those were transplanted here in the United States, and the rest of that tissue was sent abroad. Next slide.

What is the potential for transmission of

infection through corneal transplantation? The charge here today is bacterial infection and perhaps fungal infection.

There are two conditions in ophthalmology, for those of you who don't deal with this every day, that we worry about post-operatively in terms of infections. One is infectious keratitis, and the second is endophthalmitis.

I'd like to just show you a few pictures and show you what this is. Keratitis is an infection of the cornea -- next slide -- which means this is what a corneal transplant looks like, a modern corneal transplant. The central area that you see has been transplanted.

That very fine suture that you see holds it in place. It's a 10-0 nylon suture. Those sutures stay in place for a long period of time, because this tissue is somewhat unique in its avascularity. It takes a long time for healing to occur.

Now that has some implications for the possibility of post-operative infection that are not necessarily donor related, and so trying to sort these things out as to what might be donor related and what is not donor related is an issue that requires some explication. Next slide.

This is a picture that shows a case of infectious keratitis post-operatively in a corneal transplant. Keratitis is basically a bacterial infection. It causes a breakdown of the corneal epithelium and stromal involvement that you see here without evidence of deeper involvement in the eye. Next slide.

In contrast, you have a picture here of a post-op patient. This was taken about 24 hours post-op of the corneal transplant, and this patient has endophthalmitis, which carries with it a much worse prognosis, and that is an infectious condition in which there are involvement not only of the outer layer of the eye like the cornea but the interior layer of the eye.

It carriers with it a very guarded prognosis. Even though many of these eyes are saved, the visual potential is not high in many of them that have this. That relates to many factors, including the speed with which it is recognized and treated, but also to the virulence of the organism.

The organism that we most fear in ophthalmology in these cases is *Pseudomonas*, and within 24 hours, because of the liberation of the proteolytic enzymes that *Pseudomonas* has, you can

irreversibly destroy eye tissue. So that's a real concern of ours. Next slide.

Now let's consider what is the incidence of post-operative infection after anterior segment surgery. In ophthalmology that means surgery of the front of the eye, and the major categories that we fall into are cataract surgery, glaucoma surgery, and corneal transplantation.

Now the overall incidence is actually quite low. If you look at that, you can see that cataract surgery is 0.08 percent incidence of post-operative bacterial infections.

Glaucoma surgery to reduce the pressure in the eye, making a valve-like opening in the eye for aqueous to drain out, has a slightly higher incidence but still quite low. When you combine cataract and glaucoma surgery, which is what trabeculectomy is, it's about the same incidence.

Penetrating keratoplasty or corneal transplant has a slightly higher incidence of post-operative bacterial infection, but it's still quite low. Next slide, please.

This is another example of a severe case of *Pseudomonas endophthalmitis* post-operatively. Next slide.

Now what are the factors that are unique to corneal transplantation that might predispose it to the slightly higher incidence of post-op infection? These are non -- perhaps most of these are non-donor issues.

There is a prolonged healing time. When you put a corneal transplant in place, the average healing time is a year, and sometimes a year and a half, because you have to keep sutures in.

You have to keep sutures in for a long time. They can loosen up. They can become a nidus for infection, and that is frequently a site for post-operative infections, and they can occur months, up to a year or more after the surgery.

The epithelial surface is disrupted itself, which makes a good spot for bacteria to adhere, and many of the disease processes which necessitate corneal transplantation alter the surface defense mechanisms that make patients more likely to get an infection.

Finally, we typically use corticosteroids on an extended basis post-operatively, which makes patients a little bit more susceptible to infection. Next slide.

A couple of general statements. I'd just

like to share with you briefly what some of our experience is with this. There has been some interest in this recently, and just to share with you three relatively recent studies that have been done.

Now the question is: Is there a clinical utility in performing routine cultures of tissue that's taken to be transplanted?

Over the years, a number of places have routinely cultured the donor rims, as we say. Just to orient you once again, there are two ways of taking corneal tissue, one of which is to enucleate the whole globe, which has been done for many, many years, and that's the way it was done routinely prior to the last ten or 15 years.

The last ten or 15 years it's been much more common to simply excise a bit of cornea and the surrounding sclera and put that into a culture medium and to transport it in that way. We have a good culture media now which can keep the important cells, the endothelial cells of the cornea, in pretty good shape for at least a week post-operatively, and in some cases longer than that.

It relates to a question that just came up about 15 or 20 minutes ago. Where does this normally happen? Well, nowadays it normally happens in the

hospital, maybe a hospital morgue.

It may be in a funeral director's place, wherever the tissue can be gotten, because it should be gotten within 12 hours of the time of death. So it's usually in those circumstances that the tissue is taken.

Now despite the fact that I have said that it is common practice, it has been over the years, to take routine cultures, this has become a controversial issue because of a number of studies that have been done. Next slide.

The donor corneas undergo a sequence of preventive strategies designed to minimize contamination and transmission of infection, and these are the standard things that go on with other tissues such as chart review, social and medical interviews, aseptic technique and antiseptic rinse of the cadaver eye, etcetera.

These things are not particularly unique to ophthalmology from the other tissue processing. Next slide.

So you want to provide it with altering its integrity, form or function, and that means, as far as corneas is concerned, it's transparency. Next slide.

It can't be sterilized and still be viable for transplantation. The cells die, and the tissue won't live. So it is preserved in a corneal storage medium, and the medium also contains broad spectrum antibiotics to discourage bacterial growth. Next slide.

The EBAA promulgated the standards in 1980 for the practice of procurement and distribution of corneal tissue. Next slide.

These are some of the things the eye banks are required by EBAA's medical standards to have, and they are fairly standard, and I think that they are also typical of other tissue procurement procedures. Next slide.

Once again, the EBAA has a very complete procedures manual. A medical director and the eye bank director are responsible for each bank for assuring that the eye bank personnel comply with all the applicable procedures, etcetera. Next slide.

The procedures manual also talks about pre-ocular tissue recovery and donor preparatory procedures, and they are fairly explicit, and this is pretty stringently enforced.

The EBAA, in the process of certifying the member eye banks, perform site visits. There is a two

to three-year inspection cycle. At any given time, 90 percent of the members of the EBAA are judged to be in compliance with all of these.

At any given time, slightly less than ten percent, a problem has been identified, and it's usually in the process of being reconciled. So there is a continual process going on. Next slide.

These are some of the things that we do. Next slide.

And the contraindications. As was alluded to in a question just a little while ago, are there many exclusionary criteria? There are lots. These are just a few of the ones that are sort of hot issues now, exclusionary criteria, particularly the ones that relate to prion disease and to active septicemia and active bacterial or fungal endocarditis.

Social medical history is particularly important in terms of transmission of conditions like HIV. Next slide. Let's continue. Just go next slide.

These are, once more, just a little bit more about the various things that go through. You can see that in your material that you have. Next slide.

Now the issue of corneoscleral rim

cultures: The EBAA says it's optional for eye banks. What has basically happened over the last ten years is that many of the eye banks and the corneal surgeons have gotten away from getting corneal rim cultures.

There's a cost factor involved, but the main reason was that over the past 15 years there have been a number of studies looking at corneal rim cultures and seeing what relationship they had to proven cases of bacterial endophthalmitis.

The bottom line is there's not much. The culture rate -- next slide; just keep going, and we'll skip through that, too.

There is a recent study by Everts, *et al.*, that looked at this. The culture rates that have been reported range from about five percent to 32 percent positive cultures in tissue that's collected. That's a pretty high percentage in many of them.

I was one of the authors in one of the studies. We found a 28 percent positive bacterial culture in corneal rims in about 230 cases. In none of those cases was there any post-operative infection, and in most of the other studies, all of which have been retrospective, that looked back, there's been very poor correlation between what you find in the corneal rim cultures that were taken and the cultures

that you get from the offending organisms in real post-operative infections.

That speaks to the fact that one of the major sources of post-operative infections, when they do occur, is the resident bacterial population in the recipient rather than the donor. Next slide.

In this study five percent of the corneoscleral rim cultures yielded microorganisms, mostly coagulase-negative Staph. Two patients in this series developed endophthalmitis, one with Staph and one with Pseudomonas, within three months after transplant, and each had a negative culture, and neither patient's infection was temporally related to the transplant procedure. In other words, it was a long time afterwards. Next slide.

The authors of this study concluded that preop donor corneoscleral rim cultures are unreliable predictors of endophthalmitis, and the discrepancy between the results of these cultures and subsequent endophthalmitis, they believe, rendered them invalid as a quality assurance procedure. Next slide.

There are several other studies. There is one by Wiffen, *et al.*, that looked at the value of routine cultures again. This study is of interest, because it's one of the largest studies. It's over

1,000 patients that were looked at consecutively in a university setting. Next slide. This was from Mayo.

The rim cultures are available as you see here. There were three cases of endophthalmitis. The rim cultures were negative in all three cases. The rim cultures were positive in just under 20 percent of the cultures that they took in the study. Next slide.

They concluded that routine corneal donor rim cultures have no predictive value for the infective complications of penetrating keratoplasty. Next slide.

Finally, there is another study from New York by Speaker, *et al.*, that looked at some of the causative organisms of endophthalmitis following not just corneal transplant but other kinds of surgery. Next slide.

They found that the organism isolated from the vitreous, which is where you can get a positive culture in the interior of the eye, was genetically identical to organisms isolated from the patient's skin, conjunctiva or nose in 82 percent of the cases, and in two of two cases following corneal transplantation.

It speaks to the fact that the primary culprit is the resident bacterial population on the

recipient. Next slide. Next slide.

These just show you that there's been lots of studies that have been done about corneal rims at this point. Next slide.

Once again, gram positive organisms are the most frequently present on both the donor and recipient external tissues, and they are the most common causes of post-operative endophthalmitis. Next slide. Next slide. Let's just skip over that.

So the Eye Bank Association of America has an adverse reaction registry. It's been in place for a considerable period of time. It seems to be working pretty well.

We are certainly not satisfied with the fact that we have any cases of post-op endophthalmitis, but the incidence is quite low in this regard. There is more detailed information about the EBAA procedures which are very similar to those for other tissue bank operations here.

One final thing that I would leave you with is there is a study ongoing now to try to identify the predictive factors that may give a clue to a patient that's at higher risk for developing post-operative endophthalmitis, and the results are not in of that study, but it is in process right now,

and the EBAA will be monitoring that closely.

I think those are the points that I really wanted to cover here. I thank you for your attention.

CHAIRMAN NELSON: Thank you very much. Questions? Patients who get a corneal transplant -- do they have perioperative or preoperative antibiotics or is that not used?

DR. LEMP: There is some variation in that. Preoperative, no. Almost nobody does that anymore. Perioperative, yes, but they are almost never systemic. They are topical antibiotics, and they are used varying times, anywhere from a few weeks to a few months post-operatively.

CHAIRMAN NELSON: In some surgeries like C-section, you know, that's dramatically reduced the perioperative infection rate, the use of just a day or the dose or two of antibiotics, when the problem is with the endogenous flora of the patient.

DR. LEMP: We have the same experience in ophthalmology, and the use has gone way down.

DR. ALLEN: That answered one of the questions. The other one was just is it common or uncommon to culture the anterior nares preoperatively and, if there is *Staph. aureus* isolat treat that with topical antibiotics before surgery?

DR. LEMP: It's extremely uncommon. It's not done. Actually, just as a point I will tell you that as a surgeon one of the things that bothered me a few years ago was the fact that you could get contamination of the field by nasal secretions and what-not.

One of the things that I was very stringent about when we used to use a lot of general anesthesia was that they used atropine to dry up the nasal secretions, so you wouldn't have that kind of a thing as a potential contaminant. But, no, they are not routinely cultured. Maybe they should be, but they are not.

DR. HOLLINGER: Despite the recommendations and all the good information that suggests the rim cultures are not predictive, what percentage of ophthalmologists still culture the rim?

DR. LEMP: I'm not sure we have good data. Pat, do we have good data? I don't think we do have good data on that.

DR. HOLLINGER: I can tell you from Houston, I serve on a medical board of the Lion's eye bank which is one of the larger ones, I think, in the country, and about 50 percent still culture. I think we are in the process of trying to recommend -- make

another recommendation to them that they probably don't need to do so.

Some of it, I think, is because of concerns about litigation and so on, probably more than anything else. Usually, it's the older ophthalmologists and sometimes the younger ones.

DR. LEMP: Habits are hard to change.

DR. DiMICHELE: Is there any correlation data with infectious keratitis? I mean, most of the data is association with rim cultures with endophthalmitis, but what about infectious keratitis, and is there any reason to care about that, if there isn't? I mean, in other words, all this data that you have shown us for endophthalmitis, but what about infectious keratitis?

DR. LEMP: Well, number one, infectious keratitis can lead to endophthalmitis, number one. Number two, even in the absence of endophthalmitis, infectious keratitis can destroy the integrity of the corneal tissue, therefore destroy its transparency, and the purpose for which you did the corneal transplant is not served well.

We have less information about that, but we do have some information, and actually there are some slides in there that I didn't take the time to go

over that break out the incidence of keratitis versus endophthalmitis and also the relation to the corneal cultures. They are not predictive for that either.

DR. STYLES: In your experience, is keratitis more common than endophthalmitis?

DR. LEMP: Thank goodness, yes.

DR. STYLES: Then why does your registry seem to indicate that the reported cases that infectious keratitis is less common?

DR. LEMP: Because I don't think they are reported as much, because they are not considered as important, because --

DR. STYLES: So you are saying that you have incomplete reporting then of your adverse reaction registry with states. It specifically tells them to report infectious keratitis, but you are saying you suspect that it's not being reported?

DR. LEMP: That's a suspicion. I can't prove it, but i know from a clinician and from a clinical practice that what happens is that many of these cases, if you recognize and treat it with antibiotics within two days, it's gone, and you don't have tissue destruction, and you have no consequence from it afterwards and --

DR. STYLES: So you think you're just

getting -- You're getting the more severe cases, and the relatively benign cases are just being passed off then?

DR. LEMP: I think that's probably true of all reporting.

CHAIRMAN NELSON: How long -- You said the nylon sutures stay in for a year. You then take them out?

DR. LEMP: Usually, yes. They degrade over about a two-year period, about between year tow and year three. They actually break down, and then they can separate. Then a loose end sticks up and becomes quite irritating.

The real reason that you take them out at a certain point afterwards when you feel you've got good wound integrity and you've got a good scar around the edge is the fact that they exert a certain tension on the shape of the cornea, and that affects the refraction and whether you've got a lot of astigmatism or what-not, and you try to get them out so it can assume a shape you know what you're dealing with, and you see how you can correct the refractive error you've got at that point.

DR. FALLAT: How do you explain the large number of rim cultures that are positive, five to 30

percent, in view of the fact that it's stored in antibiotic solution? Is there an explanation for why you have such a high percentage of positive cultures?

DR. LEMP: Well, that -- As Dr. Nelson was saying, those cultures are taken prior to storage in the antibiotic solution.

DR. FALLAT: What about prior to use?

DR. LEMP: Well -- Excuse me?

DR. FALLAT: What about prior to actually putting it --

DR. LEMP: Sometimes they are taken, yes, in both settings. You're right about that. Well, number one, the antibiotics we use don't cover the entire spectrum that we have, and so I think that a lot of it has to do with -- The disparity in the reporting that you get between five and over 30 percent also has to do with the efficacy of the culture mechanisms that you use.

You are certainly going to get a higher positive rate if you don't use transport medium and things like that, and there's a big variation in that from where these cultures are taken. But it's very common. I think they are just contaminated, and I think that the antibiotics that are used in the solution are not completely effective in eradicating

them, really.

DR. LEW: I'm just wondering if we can learn something from the different groups, because EBAA is obviously an older, more established group than the AATB. I notice that you have already this adverse reaction reporting.

It's got holes in it, you know, as was pointed out, but can FDA learn from this and have it as a requirement for -- or request all the groups to have something set up to do this?

Also I notice the differences that your group mentions that you do go back and expect people to train everyone appropriately, and it's in your guidelines. I suspect when you go to do your reviews on site, you want to have documentation of that. Is that also required for AATB? Is that something that they want to implement as well?

Instead of reinventing the wheel, take what's good, and then elaborate that for FDA.

DR. LEMP: Good point.

DR. DOPPELT: Can I could just make a comment? In the AATB standards, they do require that each bank keep an adverse reaction file. So that information is there. They don't -- currently, they don't have to -- You know, every time an incident

occurs they don't have to report to the AATB. However, if they are an accredited bank, we would review that file when they come up for reaccreditation, which is every three years.

I think one of the issues for the AATB and for the FDA and CDC is, you know, what kind of reporting structure do you want to have? When you have an incident, when do you know about it?

Obviously, one of the messages here is that we'd like to hear about it sooner rather than later. So that's something that needs to be changed. I mean, so the data is there. It's just that it's not getting to the office in a timely fashion. So we have some homework to do.

DR. LEW: What about the training issue? Is that also a requirement, and you will check on that whenever you go for site visits?

MS. MOEW: Yes. Training is required, and training files are inspected at the time of inspection, and they are maintained and documented.

CHAIRMAN NELSON: Your data never really specified, of the keratitis and endophthalmitis, how much was -- how many incidences were believed to be because the cornea was contaminated or infected when it was put in place, as opposed to the endogenous

infections of the graft from the patient. Your data aren't too clear on that.

DR. LEMP: We don't have data that are clearer, because it wasn't looked at from that point of view.

CHAIRMAN NELSON: Are there episodes, you know, during your 40-60 year history or whatever, that it clearly was, you know, either two eyes from the same patient?

DR. LEMP: Oh, yes. But those are mostly anecdotal things that we have. Clinically, the thing that -- There are two things that we hang our hat on in that type of thing.

Number one is the proximity between the time of the surgery and the initiation of the infection. Practically all of these will occur within 48 to 72 hours of the time you do the corneal transplant.

Number two, what happened to the other eye tissue that was -- Now that's not -- The second one is not a really good predictor, because I've had my own experience with that in which back 25 years ago I had a case of endophthalmitis, a terrible case of endophthalmitis, *Pseudomonas*, that occurred, and I transplanted both corneas into two different patients

the same day. One got an infection. The other one didn't.

Now that was prior to our taking donor rim cultures. It wasn't commonly done at that time, but I meant the two donors together didn't correlate into -- didn't result in infection in both of the recipients.

DR. ALLEN: What proportion of -- Well, let me ask it a different way. How long after surgery is the patient discharged home? I assume that many of these are done in an out-patient surgical setting today?

DR. LEMP: Usually about 45 minutes.

DR. ALLEN: My question, obviously, was in terms of follow-up and where a post-op infection, even one occurring within 24 to 48 hours, it's --

DR. LEMP: Usually, typically, the patient is seen the next morning.

DR. ALLEN: But it's in an office setting, not in a hospital setting where --

DR. LEMP: That's correct.

DR. ALLEN: So it's outside of the routine infection control?

DR. LEMP: Usually, yes.

CHAIRMAN NELSON: We still have one person

that wanted to make a statement, Wilson Burgess. Is he here?

MR. BURGESS: Thanks for adding me on. My name is Billy Burgess. I'm the Senior Vice President of Research for Clearant, and we are a company that is using new methods, we think, of gamma irradiation for pathogen inactivation, and we've heard about gamma irradiation some today, and I'm in absolute agreement that conventional gamma radiation affects the structural integrity of bone.

I think by the use of antioxidants and some methods we've developed, we can maintain good structural integrity. I just wanted to show you a few slides, because we've really turned our attention to the tissue program right now because of some thoughts we had about emerging pathogens, concerns about not being able to really process aseptically material that is not sterile coming in.

You know, I'm not going to spend a lot of time on the advantages. I'm not going to spend any time on the advantages of gamma radiation. You know, the main strength is that it's not discriminatory in terms of pathogens.

If it's nucleic acid based gamma radiation or inactivate, it's penetrating which we think it's

important for the tissue industry. It has a potential to serve as a terminal sterilization.

There is no addition in our process of the addition of toxic chemicals like the psoralens that have to be removed later. It's scalable, which again fits, I think, some of the needs of tissue, and validation is relatively straightforward. Next slide.

The advantages of 50 versus 25 kilograys -- 25 kilograys is really the tops that any tissue bank, I think, would use -- comes in being able to get resistance for us, to get complete inactivation of the lipid enveloped viruses, and we've been able to get up to 6 logs of reduction in the non-lipid enveloped viruses, and to date the non-lipid envelopes aren't the real disease problems, but in terms of the potential for emerging pathogens we think the non-lipid envelopes are a concern. Next slide.

I'm not going to give a big advertisement for Clearant today, but the literature teaches against the use of gamma irradiation for biologics as well as for tissue. Our focus since we started about two years ago has been on plasma derivatives and individual therapeutic proteins.

We've been successful in a number of these endeavors, and I think we've made significant progress

on devitalized tissue. I'm not going to show you a lot of the tissue data today. We can talk about it.

I was presenting to a bunch of investors this morning, and finally relaxed for a bite of lunch, and our President, Bill Drohan, came and said why don't you see if you can get on the end of the BPAC meeting, and so there's not a lot here, and I know it's late. Next slide.

This is just a model that we use where we take a bone chamber, a piece of cortical bone, drill out holes, and then put various infections or pathogens in it. In this case, this is a vial of *Clostridium sordellii* that came from the ATTC, put that bone into the gamma irradiator, and I'll just show you some of the results that we've gotten to date. Next slide.

This is inactivation porcine parvovirus in that bone, almost 6 logs of inactivation of the toughest virus we have in our hands to inactivate. Next slide.

This is the *Clostridium* experiment. We took the spores, put them in the bone, and then after irradiation, there's zero, 25 kilograys. That's two and a half megarads or 50 kilograys, 5 megarads, then cultured those under anaerobic conditions.

What you can see is that gamma irradiation is very effective in killing. We get about 8 logs of reduction in terms of the dilution series where we see *Clostridium* growth. You know, that's the *Clostridium* growth there. We get about 8 logs of reduction, but at 25 kilograys or two and a half megarads, we can still pick it up in the stock in the first one to ten dilution.

Contrast 50 kilograys. We are unable to detect any residual *Clostridium* growth. The next slide just shows an attempt to quantitate a little better. These are the undiluted plates after 24 hours, a lawn of *Clostridium* growth. We can still see the beginning of a lawn after 25 kilograys, no growth after 50. Next slide.

This is the 10^4 dilution, unirradiated, 25 kilograys, were gone by 10^4, and 50 kilograys, obviously, no growth. Next slide.

10^6 dilution, still pick up colonies in the unirradiated samples, none in the 25 or 50, and then maybe one more slide.

Then, obviously, you know, *Staph. epidermis*, *E. coli* -- those are all easy to kill with gamma irradiation. We can kill everything. We can spike into the assay at 25 kilograys, but we do have

this residual *Clostridium* spore content after 25 kilograys that we can't pick up with 50 kilograys of gamma.

This was done at room temperature. These were irradiated on dry ice where you can see the log reduction in the 25 kilograys, a little more problematic.

So that's really all I had to share, and thanks a lot for giving me a chance to share some data. But I think there are some effective means to deal with the *Clostridium* and other resistant spores.

I know there's not a lot of data that we put out there yet on the utility of gamma for doing tissue. That's forthcoming. We've got a number of tissue banks we are working with on this problem now.

DR. HOLLINGER: Did you say you could use 50 kilogray?

MR. BURGESS: We can. Everything that we've done has been -- We didn't want to be another step in the pathogen inactivation. So the 25 kilograys is great for most bacteria. It's pretty effective for the envelope viruses. Envelope viruses, we've got effective means in the plasma industry at least to deal with those, but the recoveries that we are seeing with 50 kilograys on things like IVIG are

greater than 95 percent.

In terms of the tissue of the bone right now -- You know, we can take conventional gamma, irradiate bone, 25 kilograys, there's a 25-30 percent reduction in the structural integrity. We can reproduce the data that's in the literature pretty well.

By the use of these antioxidants during irradiation, at 25 kilograys the integrity in structural testing is indistinguishable from unirradiated statistically, and we are at about 90 percent retention of structural integrity after 50 kilograys which is well within the variance that we see just from different tissue samples.

CHAIRMAN NELSON: May I ask, were all tissues -- It was pointed out that more tendons and -- was a bigger problem, actually, than bone. That's true for all the tissues? You can do the same thing?

MR. BURGESS: I can't tell you we're there on tendons yet. I mean, we've been mostly active in the bone program, because that's the biggest part of the industry. But soft tissues are certainly on our list.

We've got -- We haven't done a spike in the soft tissues. We've got some recovery data.

CHAIRMAN NELSON: How far away are you from marketing or offering or FDA licensure or whatever it takes to have this available, do you think?

MR. BURGESS: We've got one tissue bank that we are -- I think we've agreed to everything but the financials in terms of -- and in terms of plasma, fractionated are the same deal. We're not negotiating the science anymore. Other people are doing negotiating the financials.

So with tissue we think it has potential to be soon.

DR. DOPPELT: I do have a question. I may have missed this. What are you adding as an antioxidant?

MR. BURGESS: Well, it's not a cookie cutter sort of procedure. Depending on the therapeutic -- You know, there are two goals. There is primary damage from gamma irradiation which we can't control but doesn't really damage proteins. It hits nucleic acid.

The secondary damage from gammas is the problem, and that's the free radicals, reactive oxygen species that are generated from the interaction of gamma photons with water and oxygen.

So there are two approaches Clearant has taken. One is to control things like moisture, water to reduce the potential to generate those free radicals, and then by the use of protectants or antioxidants to protect the protein from any free radicals that might be generated.

The most effective one that we've used is ascorbate, which -- that's its normal function in our bodies, to protect us from cigarette smoke and other oxidants, and it proves to be an effective protectant for gamma irradiation as well.

DR. DOPPELT: So what you are saying is that, for example, bone morphogenic proteins and other proteins would not necessarily be affected by the radiation?

MR. BURGESS: Yes. We've done some work on -- With tissue it's hard to say which BMP or which factor you are going to work with. We've done some -- certainly, some work with the purified individual factors and can maintain the mitogenic activity, the differentiating activity of those proteins in a test tube.

For tissue, I've shown you the structural data. We've got some cell culture assays that you can look for the BMP type activities *in vitro*. The real

test is to do ectopic implants and show that you can stimulate ectopic bone formation in animal models, and we don't have that data.

CHAIRMAN NELSON: Do your procedures have to undergo like FDA licensure or be acceptable to AATB or what are the criteria to get this to be an available standard routine, ordinary procedure?

MR. BURGESS: Tom Lynch, who used to be at CBER, is head of our regulatory, and I'd really rather have him speak to those. But, clearly, there will be FDA review for the therapeutics, the biologics. The tissue depends probably on the timing.

CHAIRMAN NELSON: Dr. Solomon, our instructions were to have a discussion this afternoon. I think we've had a discussion. But is our discussion adequate for your needs or do we need to do or say or consider anything else? Okay.

So for once, we have met our target. So we'll see you in June, I guess.

(Whereupon, the foregoing matter went off the record at 3:35 p.m.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: FDA CBER

Before: Blood Products Advisory Committee

Date: March 15, 2002

Place: Gaithersburg Holiday Inn
Two Montgomery Village Avenue
Gaithersburg, Maryland

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.

Kay Fouts

Kay Fouts