SPEAKER: Good afternoon, and welcome, and happy holidays from CTSA to all of you. Thanks for being here today, and not off sledding or having snowball fights, as you might have wanted to do.

It's our pleasure today to welcome Dr. Moran, to talk to us about the development of the Hand and Face Transplantation Program here. Dr. Steven Moran is Professor of Plastic Surgery, and Professor of Orthopedic Surgery at Mayo Clinic in Rochester, and also a staff surgeon at the Shrine Hospital for Sick Children in Minneapolis.

He's presently the Chair of Plastic Surgery and the Director of Mayo Clinic's Composite Tissue Allotransplant Program. He attended Williams College in Williamstown, Massachusetts, for his undergraduate degree, and then the University of Rochester in the other Rochester, where he obtained his medical degree.

He remained there and trained in the Integrated Plastic Surgery Program there, and finished his training at Mayo Clinic, where he completed a one-year Hand and Microsurgical fellowship under the direction of Allen Bishop.

So it's our pleasure to welcome Dr. Moran today.

[APPLAUSE]

STEVEN MORAN: Good afternoon. Thank you for inviting me. I'm presenting not only for the Division of Plastic Surgery, but also for the Center of Regenerative Medicine and the Transplant Program here.

There's been a lot of publicity and press about hand and face transplantation, and we'll just take the first 20 minutes to 30 minutes, just to go over what is involved in hand and face transplantation. And then just talk to you about how we've applied this program here at Mayo Clinic, and what this means for the Clinic moving forward in the future.

When you perform a hand or face transplant, it's a little bit different than a solid organ transplant in that you're taking a piece of tissue that has more than one type of tissue in it. So we have in a hand or a face, bone, muscle, and skin, and we also have a large nerve component.

In order for these transplants to be successful, you have to have neural regeneration into the transplanted component. So this is an example of the first US transplant here, from Louisville. And this is his hand being put back on. And you can see him in the picture there, just a few days after the transplantation. He can't feel anything in that hand. He can move the fingers somewhat. But for the hand to be completely functional, we really need to recover about eight millimeters of two point discrimination within that hand to consider it a success.

So since that early transplant here in the United States, and the first one performed in 1998, there's been over 65 hands and upper limbs that have been transplanted across this world, into Europe and Asia. And really composite tissue transplantation is now really an established means of upper limb reconstruction. We no longer consider it an experiment.

We know that you can do it. We have patients now that are out beyond 12 years following limb transplantation. In 2002, a worldwide registry was established to track all of these patients moving forward. And I'll be presenting most of the data, and the published datas will be coming from that study, in particular.

So if we look at patients from 1998 to 2010, there's been 49 hands and 33 patients. A majority of them are occurring unilaterally, initially, and then moving to bilateral hands within the past seven years. The average age of the patient at the time of transplantation has been 32-years of age. In follow up now, in this publication that we're talking about, extended from one month through 11 years.

The time from injury was from two months to 34 years. And we now know, based on the second patient that was done in the United States, that if we perform PET scans and MRI of the brain following transplantation, we can see that there are portions of the sensory and motor cortex that are actually reactivated following a transplant of an upper arm, which is quite remarkable, considering we didn't think that the brain had such neuroplasticity. But we now know that this is possible.

46% of the transplantations have been performed at the level of the wrist. And you can see a partial hand transplant here. The more proximal you go in the arm, the more difficult it is to regain meaningful function. Nerves regenerate at about the rate of an inch a month.

And so in order to get a nerve from the upper arm all the way down to the hand, you can see that that will take many cases. Over a year. So the closer you are to the hand, the better the function will be.

We've had the technical-- and I should mention before I go on that there are some graphic pictures in this, unfortunately.

[LAUGHTER]

I know you're all eating lunch. Hopefully, that won't bother you too much.

This is actually one of the first forearm transplants I performed. This was a young boy who got his hand caught in an apple picker. And we've had the capability of doing microsurgery and putting arms back on since the middle of the 1960s. And in fact, the first reported case was a thumb transplant in 1965.

So I just put this picture up here to explain a little bit about what's involved. You can see, first of all, when we do traumatic amputations, it's not pretty. There is often a soft tissue deficit. This is the patient at seven days.

We were able to put all the tendons back together, put the nerves back together. But you can see there's a soft tissue deficit here. This will be covered with a skin graft and take some time to recover.

But when the amputation is at the level of the mid-forearm, all of your muscles that control grip, and extension of your fingers are located up here in the proximal forearm. So you can see, even though that this child can't feel his hand at all, he can still make a rudimentary grip, because his muscles are located proximal to the level of injury.

It'll take him several months to recover feeling. And without feeling, he'll rely on his vision to use the hand. And so, really, it could be argued that it's no better than a prosthetic, unless we recover some form of sensation. And that will be important as we talk about the ethics of this, as we move on.

This is a hand that was transplanted at the University of Pittsburgh. We've been very fortunate to be able to work with this group very closely. You can see in this circumstance, it is confusing, but it's not as gruesome as the case we've just presented. When we go and procure the arm from the donor, we use a very standardized approach. We take extra tissue. We rarely have a tissue deficit. And when we label each one of the tendons, you can see there's a lot of structures in there that need to be hooked back up moving to the donor.

So when we're talking about hand transplantation, in many cases, this can be a technically more simple operation than that of a true hand replant. And you can see, in this case again, from Leon, France, that they actually have extra tissue present, extra muscle bulk in the transplanted arm on the right-hand side.

The technique-- we'll go back here. We'll run the video here. Involves two teams. If you're doing both extremities, then you'd have four teams. One team procures and then prepares the donor. And the other team prepares the recipient. And the recipient preparation, in many cases, is much more difficult, because you have to find adequate blood vessels and nerves.

The bones are hooked back up using standard plates and screws, as we would for any fracture. The blood supply is then re-established. You want to do that as quickly as possible, because the hand is suffering from a lack of blood flow. Then you reestablish the venous outflow. And then the muscles are repaired, or the tendons, depending at what level. And, finally, the nerves are repaired.

And this is all done under the microscope. And, again, having two teams working simultaneously significantly cuts down on the time for these procedures, which can still extend beyond 12 hours. This is just showing the nerves being put back together.

And, again, as I showed you in that case of that young kid who had his hand caught in the apple picker, that if the transplant is done at the level of the mid-forearm, or the distal forearm, the patient can move their hands as soon as they're in the recovery room. And this has been the experience of both the French group and the Pittsburgh group.

The patient can actually move their hand, in some cases, after several years of not having a hand. They won't be able to feel it, however. But the brain is able to reactivate and fire those muscle groups that haven't been used in several years.

So one of the issues we have to deal with technically is this cold ischemia time, the time from when you take the limb to when you reestablish blood flow. The longer the arm is without blood flow, the more toxins you produce in the muscle. So it's critical that we keep that time down to approximately six hours. And that has consequences in how far we can travel with the arm back to Mayo Clinic.

And again, the sequence is bones first, followed by the arteries, veins, tendons, nerves, and, finally, the skin. The duration of the operation, for most unilateral cases, extends between eight to 18 hours. For bilateral cases, it has extended beyond 24 hours.

This is a transplant. So just like with a kidney or a heart, patients need to be on immunosuppressive medication. The skin happens to be one of the most immunogenic organs in the body. And that's important for monitoring these patients.

But they do have to be managed with an induction therapy. So as they're going to the operating room, they're given high doses of medications that will suppress all the circulating white blood cells and T cells in their body, so that they will accept this organ as their own.

There have been several different experimental protocols to try to induce things called tolerance, and chimerism, which is tricking the body into thinking that this arm is yours. However, none of these have been truly successful. And probably most, in my opinion, most experimentation on immunosuppression should not occur in patients that are undergoing hand and face transplant, because the numbers are so small.

We have other groups that undergo thousands of transplants a year, such as kidney transplant. We really should reserve experimentation on immunosuppression for those groups of patients.

So this is just an example for those of you that work with a lot of transplant patients on what types of induction therapies have been used. Again, most involve a antithymocyte globulin, but others have used monoclonal antibodies.

The maintenance therapy these patients all need to be on, at the Mayo Clinic, they will be on a triple drug therapy that consists of steroids, a tacrolimus, and MMF. These are all immunosuppressive medications. Interestingly, tacrolimus accelerates nerve recovery. We're not quite sure of the exact mechanism.

But instead of growing an inch a month-- remember I talked about the nerves. They grow a millimeter a day, or an inch a month. They can actually grow four millimeters a day. So this is actually beneficial for the patients in recovering nerve function.

So as I mentioned, the skin is the most immunogenic organ on the body. So when these patients do reject the hand, many times they reject at the skin first. We have a variety of different pathways that we're trying to block to prevent the immunogenic cells, the TMB cells, from recognizing the transplanted hand is foreign.

But patients usually develop a rash. And most patients, despite the medications that they're on, will develop at least one episode of acute rejection within the first year. And, as you can see here, up to 10% of patients can experience four or five episodes of rejection. Fortunately, this occurs in the skin first. They get a rash. It looks like psoriasis.

You can then make the diagnosis with a skin biopsy. And we will be working closely here with the dermatologist to make this diagnosis. But in several patients that have had face transplants, they've actually put a separate skin paddle from the donor, usually in the groin, so that you don't have to do biopsies on the face itself. And you can simply biopsy the skin paddle that was taken from the donor in the groin.

They have found that those island flaps, as they call them, actually will reject about 48 to 36 hours before the face. And the reason for that, again, you in the audience that are in the transplant program, it's probably because we're carrying bone with the hand and with the face.

And bone contains bone marrow, which contains the potential to create a T and B cells, and maybe a local environment that is more tolerant to rejection then the skin paddle itself. So it's been fortunate for those patients, because you can pick up the rejection sooner, and provides us the means of treating these patients.

And treatment usually consists of IV steroids, or topical steroids to the hand. There's also topical tacrolimus, which you can use directly on the hand itself to help decrease the episode of rejection. And these are the standard treatments and the percentage of patients that have been placed on these medications to control rejection.

Now when you have a rejection episode in the kidney or in the heart, that organ loses a component of its function. So in the kidney, that's clearing toxins from the body. And we measure that the GFR, the glomerular filtration rate.

In the hand, we have found that despite five or six episodes of rejection, the hand does not lose function. It doesn't lose the ability to recover feeling or sensation, and the muscle function hasn't decreased following these episodes of rejection. And we're not entirely sure why that is, but it does provide us some flexibility in treating these patients.

Many of these patients are not sick. They don't have the requirement for dialysis, like a kidney transplant patient. They don't suffer from congestive heart failure, like a heart failure patient. So you're taking, usually, a young, healthy patient and you're making them feel sick by having them take these three medications every day.

And that's one big downside, and one ethical debate, regarding hand and face transplant. The other problem that these patients will experience is complications with opportunistic infections, and metabolic complications. The medications that they are on, in addition to suppressing their immune system so they won't reject the organ, is that they are more susceptible to different types of infections that you or I are not normally susceptible to.

But this is just a list of the infections that patients most commonly suffer from. CMV, Clostridium difficile, Herpes infections, cutaneous fungal infections can all occur in these patients, and they have to be aware that before they undergo the operation.

And then metabolic complications will probably develop in about 50% of patients. The most common is probably development of diabetes or hyperglycemia. There has been increasing creatinine values. No patient has undergone frank kidney failure. But there has been one reported case in Europe, just recently, of a patient developing lymphoma. So also the possibility of developing cancer following immunosuppression.

In terms of graft loss, or the hand or face failing, there have been very few cases. And if we just look at hand, there have been just two cases. The first case was the very first patient that was transplanted in France in 1998. The patient stopped taking his medication, and he rejected his arm, as you would expect.

The second case occurred in a patient from Louisville, who had the arm for 28 months. He was tapered to monotherapy. And, at that time, the patient underwent a rejection of the arm. Interestingly enough, after the rejection, he asked to be transplanted again.

Probably though, realistically, that's not possible. Once you transplant a patient, you expose them to several different antigens. And it would be very difficult to match the patient a second time for a second transplant. So that's an important concept to think about as you think about the ethics of this procedure.

Patient survival has been 97%. One patient did die. This was a patient in France that underwent a bilateral hand, both hands, and face transplant. Died 65 days after the transplant because of a pseudomonal infection in the airway. Pseudomonas is a big problem in burn patients. This transplant was done very early on in this patient's care, and perhaps too early.

We exclude from this data-- what I'm telling you now is all the transplants that have been done in China, they're excluded from the registry. One, because they don't report. But also, because their patients are not given lifelong medications. In many of those patients, we don't have the exact numbers who have rejected, and have had to have their arms removed. Again, just emphasizing the importance of taking these medications throughout the patient's life.

Again, current graft survival is 96%. So, again, we have data extending out beyond 12 years now. This is very effective. And those survival rates are in line, if not better, than many of the data we have for kidney survival.

But does it work? And in looking again at this database, protective sensibility, the ability to feel sharp, and hot and cold, is present in 100% of patients. Even those patients that have had transplants up above the level of the elbow.

Tactile sensibility is seen in 90% of patients. Discriminative sensibility, the ability to tell between a quarter and a nickel, in 72%. The ability to recover gross hand function, what I call extrinsic muscle recovery, to make a gross grip, has been seen in all the patients. The problem is intrinsic muscle recovery, fine motor function within the hand, is not present, if you have a transplant done above the elbow. And that's something you have to be upfront with, with the patient. But 70% of these patients have been able to return to meaningful employment.

There has been a functional grading system that was established by the World Society for Transplantation that looks at appearance, sensation, movement, psychological and social acceptance, daily activities, as well as the patient's own satisfaction ratings. And it's broken down into four grades, as you can see there.

If we look at all the patients from 1999 moving forward, this is the unilateral transplants. You can see that was really only one patient that was graded as poor. And if we look at the bilateral transplants, only one patient that was graded-- graded themselves as a fair outcome. So, overall, patient satisfaction has been very high, as well as functional outcome.

And this is just a longitudinal outcome study. Looking at, on the top is the hand transplant scoring system. If that goes up, that's a better score. And then on the bottom is something we call the DASH scoring system. That was actually developed here by Peter Amadio. It's a validated upper extremity function of transplant scoring system. And it looks at the elbow, hand, and finger function.

And the patient scores it themselves. And as the score gets lower, the patient is doing better. So you want to see the top graph moving up, and the bottom graph moving down. And, as you can see, the patients that have been out the longest with their transplants are doing the best.

And then there's a comparison of bilateral patients on the other side, really showing that there is not a significant difference in right or left hand transplant, when you're looking at how the patient does between the dominant and non-dominant hand.

So, in this recent review in 2012, Jensen did a systematic review of all the literature, trying to put together all the different scoring systems, in all the patients. He was able to find 27 articles, out of 247, that were relevant to this study. And of those, better than 75% of the recipients reported improvement in cosmesis, quality of life, sensory function, and social outcome.

Most hand improvement is experienced during the first three years, and then only minor improvements are experienced after that. And, again, discriminative sensation is decreased, as well as the intrinsic hand function in patients that have transplants that are above the elbow.

One of the big factors that has come out of these long-term outcome studies is that success depends on patient selection. Those patients that are going to reject, or not take their medications, are going to do poorly.

And one of the most important parts of the transplant team is the transplant psychiatrists. We have an excellent one here, Sheila Jowsey. And she's been working with the international community, and coming up on validated, pre-operative assessment for these patients to make sure that they are compliant, that they can form a good alliance with the physician, and that they have an adequate emotional development to tolerate rejection episodes, and again, understand the fact that they have got to take three medications for the rest of their life.

So if we look at all the data that we have published so far on hand transplantation.