SPEAKER 1: Good afternoon, everyone. It is really with great pleasure that I'm able to introduce Dr. Tom Brott today. He has consultanted in the Department of Neurology at Mayo Clinic in Florida. He serves as the Eugene and Marcia Applebaum Professor of Neurosciences. He and his stroke team led this the first in human studies that found that tPA was an effective treatment for early onset ischemic stroke.

Currently, Dr. Brott is the National Principal Investigator for two NIH-funded clinical trials of stroke prevention, and is the National Co-Principal Investigator for Strokenet, an NIH-funded multi-hospital network for stroke research. Dr. Brott was Dean for Research at Mayo Clinic in Florida from 2006 to 2014. He has served as chair of the Stroke Council of the American Heart Association, Vice Chair for the National Stroke Association, and Chair of the Advisory Committee for the Neurological Devices Panel of the FDA. In 2013, he received the American Heart Association Clinical Research Prize, and in 2015, he was named Distinguished Investigator of the Year at the Mayo Clinic.

Dr. Brott has published more than 300 articles, book chapters, editorials, abstracts, and letters. So please join me in giving Dr. Brott a warm welcome.

[APPLAUSE]

THOMAS BROTT: Thanks, Ricky. It's a delight to be here from Florida. I'm from Chicago, and so it's not too much of a transition for me. And I really look forward to speaking with you today.

Here are my disclosures. Actually, disclosures for CCaTS. I really have no disclosures. These are our learning objectives, and we're going to be very quick to see if you're speed readers on this. And so we're going to talk about translation. That's what this lecture is all about.

And I have maybe a little different point of view. I believe that when we translate a drug, it's the ultimate translation is when it hits Walgreens. When we translate a device, again, the ultimate translation is into the cath lab. And for our diagnostic devices, the ultimate translation is when that device reaches radiology or whatever department that diagnostic device is used for.

So how do we make that final step in translation? And for some of you, this will be very elementary, for others, it will not. The FDA is the final common pathway to translate our scientific knowledge to the patient. An investigational new drug, a license is required to administer an investigational drug to humans.

So you have to have that to do a clinical study. An IDE, Investigational Drug Exemption, allows an investigational device to be used in a clinical study. And to be new-- to be marketed, new drugs and new devices must go through the IND or IDE process at FDA, and be a judge by the FDA to be safe and effective before they can get to the bedside.

So we're going to talk about a drug and we're going to talk about a device as case studies in going from basic science to the bedside, in which you can see here on the left is the basilar artery up against the brain stem. And what you can see a little bit is a clot, which is obstructing blood flow to the brain. Here is the vessel opened up and you can see the clot is a tenacious, jelly-like substance.

An important part of this slide is the fact that the wall of this vessel is translucent, and that's because it's narrow. Very different from the coronary artery. So for example, the middle cerebral artery, one of the main arteries inside the brain, has the same diameter, internal diameter as a coronary artery, which is 3 millimeters, or a little bit thicker than a nickel on its side. But the muscular wall of the coronary artery makes interventional procedures and devices much easier than they are with the brain.

And here is a look at the brain. If you can imagine that this person is looking right at you, and the right eye is here and the left eye is here, here is the left internal carotid artery, here is the anterior cerebral artery on the left, the middle cerebral artery on the left, and you can see that there is an occlusion. And that occlusion is what causes stroke. So one enemy is the clot.

Second enemy is the clock. The brain has no tolerance for ischemia. We all know that with cardiac arrest, it may be 10 minutes, may be 15 minutes. There was a remarkable case published in the Mayo Clinic proceedings just a while ago with 96 minutes, which is absolutely remarkable. With stroke we have more time depending on collaterals, but this is a big enemy and continues to be a major enemy in the treatment of stroke, which today is the number four killer in the United States and the leading cause of adult disability.

So here's what a stroke looks like if you don't open up that clot. This is magnetic resonance imaging. And again, imagine that the person is laying on his back, his or her back, and the legs are coming right out at you. OK? By convention, the right is on the left and the left is on the right. OK? So this particular individual has a left middle cerebral artery infarction.

This is diffusion weight and imaging, which is like litmus paper for injury to the brain. Within probably 20 to 30 minutes, diffusion weighted imaging will begin to show ischemic injury to the brain. This is called the flare image. You can see it is a much prettier image with regard to anatomy. And you can see, again, the area of infarction.

Once we have gone from-- once we get to a well-delineated, diffusion weighted abnormality on the brain, that brain is essentially gone. It's dead. That's what we have to try to do something about.

Wouldn't it be nice if our brains grew from century to century? But they don't. And so we really need to use technology. And what role did technology play in these two treatments, the drug in this device that I'm going to tell you about?

Well, 1947 was a very good year. In 1947, John Bardeen, who by the way was one of the few scientists to win two Nobel Prizes, John Bardeen, William Shockley, and Walter Brattain invented the transistor while at Bell Laboratories. They won the Nobel Prize for this invention. And we went from vacuum tubes, which were fragile, large, undependable, to transistors, which changed the world with regard to electronics.

In the same year, Tage Astrup, in a series of papers in*Nature,* discovered what we now call tPA. He named it Fibrokinase. And even though he was not a clinician, he understood that dissolving a thrombus, that blood clot that you saw in one of the earlier slides, could be done by using the physiological activators of the natural fibrinolytic system, such as tPA, rather than the final lytic enzyme, plasmin, on which so many hopes lay at that time. So he was a true pioneer in the laboratory.

In the early '50s, the next big advance for stroke came from Robert Noyce and Gordon Moore. They invented the microchip. They also founded Intel. Dr. Noyce actually is from a town about 180 miles directly south of Rochester. He grew up in, well, let's see, what's-- Grinnell, Iowa. And I think he went to Grinnell for college, and ended up at MIT and other places.

Dr. Moore, his partner and co-founder, he authored Moore's law. Now if you Google Moore's law, you'll see different definitions, but the actual definition was the number of transistors per square inch on integrated circuits doubles every year. And that's been gone on to be expanded that basically computing power doubles every year. But certainly, from the time these guys put together the first microchip until maybe today, maybe a few years ago, Moore's law has held sway in the field of basic electronics.

Another pioneer was Godfrey Hounsfield, and he invented the CT scan. At the time CT scan was invented, there was no way to look inside the brain. We only had indirect methods by putting air into the ventricles, the cavities of the brain, by putting radio pharmaceuticals into the brain, and basically, looking at ink spots, and angiograms, looking at blood vessels and how they may be distorted. All the views of the brain were indirect. We couldn't tell a stroke that was from a blockage, an ischemic stroke, to a stroke that was from a rupture of an artery, cerebral hemorrhage.

And here's a CT scan. And CT scans show calcium. And again, imagine that the legs are coming out towards you. So the right side of the brain is here, the left side of the brain is here. This is the cerebellum, a balance organ at the back of the brain, and you can see this area of whiteness or increased density-- not as dense as bone, but increased density, and that's blood.

And the CT scanner allowed us for the first time to not only look inside the brain, but immediately, immediately be able to visualize bleeding within the brain, and therefore, sort strokes out. About five out of six are from an occlusion, that clot that you saw at the beginning, and about one out of six are intracerebral hemorrhage, which this CT scan illustrates. You could see that if you have a material such as tPA, then the goal is to lies clots. It's not the kind of medicine you want to use for this condition.

And here is the first CT scanner in the world. And I happen to be here. You can't, I mean it's-- when you look at that, it's almost a little embarrassing. But I was a medical student on a fellowship from University of Chicago the summer that this machine was installed in the radiology department here. Well, I guess the mail building's over that way, but in the mail building. And as of a few months ago, it was still there on display. I don't know if it still is. Is it in the hallway?

SPEAKER 1: It travels sometimes.

THOMAS BROTT: But if you get a chance, you ought to go up and take a look. This machine truly changed the world. There's just no doubt, it changed the world. And the first machine was right here at Mayo Clinic.

About the same time the CT scan was invented, Dr. Collen, he went beyond Dr. Astrup and basically showed the mechanism of tPA, how it activated plasmin, and how it resulted in clot dissolution. And we won't go into the details, but if you are interested, all you have to do is Google Collen or tPA and you can see exactly what happens. The idea is that tPA, which is produced in the body in endothelial cells, activates plasminogen, which then activates-- is activated to become plasmin and lyse its clots. When we give tPA, we give about 2,000 times the concentration of endogenous tPA.

Dr. Collen just a few years later then developed a method to manufacturer tPA with cells, melanoma cells, E. coli cells, and other cells. And E. coli cells, at that time, were the main source of the production for tPA, which could be made in pharmacologic amounts and tested in humans.

And in *Science* the next year, Justin Zivin, with the rabbit model, showed that tPA could lyse clots in this rabbit model of ischemic stroke. Very shortly thereafter, tPA was studied for myocardial infarction, and was approved for treatment of myocardial infarction as effective. And in the story that you're going to hear, we're kind of moving from the IV to the endovascular.

Cardiology has made that move about a decade earlier, in part because it's easier, they've got a very hearty vessel that they can instrument. But today, with an s-- what we call an ST elevation myocardial infarction, endovascular treatment is the standard of care. And tPA is only used in that setting when endovascular therapy is deemed, either it's not available or it's deemed inappropriate for the patient.

In 1986, the Neurological Institute at the National Institutes of Health, they funded a pilot study, basically, a phase 2 trial to see if tPA could be given safely. And here's where technology came in yet again. That's a cell phone on the left. That's my cell phone. I can tell you that that cell phone weighed about three pounds.

When I put it in the basket on my bicycle, it actually, you know, you had to be careful because it could, you know, weigh the bicycle over. There are so few cell phones, I couldn't talk to anybody. The only people I could talk to were people on regular phones because we had so few towers and so few people had cell phones.

But this phone was absolutely essential in, of course, the electronic revolution, which we all know about today. I mean, look when a plane lands. My goodness. When a plane lands today, if everybody isn't doing this, you figure maybe they have a problem. But this was what it was like in 1987.

And how did technology help? Well, first of all, you can see this is a phone bill. And it's in 1989. And you can see these amounts. We used to have to pay per call. This call was $1, and it was for three minutes. And so your bills could mount up.

But luckily, we were funded by the National Institutes of Health. They paid for the phone. They paid for the phone bill. And it was, in terms of laboratory equipment, and as dean, I had the opportunity to sign off, as Sundeep knows, on equipment that would knock your socks off in terms of its price. But as a piece of equipment, this equipment was absolutely, absolutely priceless.

This is my home number. I guess I was calling home. But let's just go down here to February 20, OK? And you can see that there are a series of phone calls on February 20. And if we look at the times-- 7:18, 7:19, 7:23, 7:24, 7:27, 7:37, 7:41, 7:42, 7:50-- what is that, eight calls over 15 minutes? Because I'm in my car driving to a hospital in northern Kentucky, which is right across the Ohio River from Cincinnati. And when I would get a page, we had to treat the patients within 90 minutes. And those of you who have familiarity with CT scans know that in 1989, the CT scan took about 15 to 20 minutes. So now you're talking about trying to treat a patient basically in an hour, OK? And that includes getting informed consent.

So these phone calls, when the page would come in, we wouldn't even answer the page. We would hop in our car, because we went to 12 different hospitals, and we would call the emergency department, we'd call the pharmacy, I'd forget the number of maybe the X-ray, which, that's the main number. So then I would get the right number, call X-ray, and so forth. Make these serial phone calls to get everything going so we could treat the patient rapidly. Basically, parallel processing while I'm in the car.

With this method, our team was able to treat people very quickly. In fact, we treated one person within 90 minutes who had a stroke on a Delta airliner. I wonder, well, why do I go and speak to the life squad at the airport? Because I went to all the life squads in Cincinnati and Northern Kentucky. And I figured, well, I'll go. They have beer, they have pizza, because this is what they do at night.

And lo and behold, the patient has a stroke. The wife notices it immediately, tells the stewardess, who tells the captain, diverts the plane to Cincinnati. They land in Cincinnati, which is in Northern Kentucky, and take the patient to the hospital. All the while, we're doing this kind of parallel processing, and we were able then to treat the patient.

We couldn't have done it without technology. And also team. Here's the patient who was treated within 90 minutes. Here's an emergency room nurse. And at that time, we had over 500 emergency department nurses on our mailing list. Remember, we didn't have email. So we had to use a mailing list. And here are two EMTs. And I can tell you, they became very engaged when they saw what we did, with that the drug seemed to be working. Here is an emergency medicine physician, and at the time, that specialty was just coming into its own. Course, the patient in this is my son, I think.

[LAUGHTER]

So what about it? Did it work? Well, this is a meta-analysis, which includes all the studies in tPA. And you can see here that this includes 2,776 patients. And if the patients were treated within 90 minutes, because after our pilot studies that showed it was safe, of course, we had to go on per the FDA to phase three, randomized controlled trials. And these trials were all randomized controlled trials. And the odds ratio for a favorable outcome compared to placebo was 2.8, and you can see the confidence intervals, the 95% confidence interval.

So basically, it was the 95% confidence interval was that your odds were twice as good for an excellent recovery if you could get treated in 90 minutes. Now when we're out to 90 to 180 minutes, look at that 95% confidence interval. We're now down to 1, OK? So today, anybody that you know who has what looks like a stroke, don't waste a minute. Don't waste a minute. Time is the enemy. So the results were published to the *New England Journal,* and you can see the number of citations down at the bottom.

The drug was licensed by the FDA as safe and effective. So it went through the entire process. And continues to be the standard of care for stroke today.

Lessons learned. Technology is an excellent partner. Time is a brutal taskmaster. And in neurology, we say time is brain. Networks and teams can expand what you can do. Even Mayo Clinic can no longer provide enough patients for clinical trials to really get to the phase three process for just about anything. And Dr. Koslow or others may know of phase three trials that are-- that are limited to one medical center, but they have to be very rare today.

The next chapter-- and this to me is very interesting. You know, I'm a neurologist, I play golf. The only thing I know about medals is that I used to use a driver that was wood, now I use a driver that's titanium. But this gentleman here was at the Defense Department, and his job was to develop nose cones for rockets that would resist heat. And while he was doing that, he came up with an alloy called nitinol.

And you can't really see this here, but some of you may be able to read it. Can anybody read that? It says, innovations. Now this was a straight wire, an absolute straight wire, loose as could be, with a small current. It turned into the word innovations. And Dr. Buehler was a pioneer in metallurgy and imparting memory to metals.

Here is a stent. At the bottom, that's not shadow. At the bottom, that's what it looks like when you put in. And boom, that's its memory-- curved, and basically, it's holding back clot. The first stents were successfully used for occlusions of the coronary artery. And you can see the stent is being placed here. There's a balloon inside. The balloon dilates the coronary artery. The artery is now somewhat open.

This is kind of idealized. It's usually not quite that open. The balloon is removed, and the artery is open. This was a true revolution in cardiology. At the time that cardiac stenting was introduced, IV tPA was the standard, but it was ineffective in many, many patients.

Angioplasty with balloons then followed. So you had the balloon, which you see in the middle figure, but no stent. And a problem with that approach was reocclusion. The rough endothelial edge and the clot were just too fertile for formation of platelet, platelet thrombi and maturing into occlusion of the lesion. And reocclusion really made angioplasty, or really limited the application of angioplasty. Stenting changed the field, and it's now the standard of care, as I mentioned, for ST elevation MI worldwide.

What about the brain? Because that's what really counts. You know, the heart's important, but the brain is what makes us who we are. Well, stents were then introduced to the carotid artery. And the carotid arteries, there's one on each side and they supply about 75% of the blood to the brain. The areas of occlusion, stenosis, are usually caused by atherosclerosis, which happens at bifurcations. This is the internal carotid artery.

And what's done here is that a catheter is put past the area of narrowing and a little kind of umbrella is opened up. Then the balloon is put in, opens up the narrowing, and you can see, those of you with good eyes can see that there are little particles that travel north toward the brain. We don't like that. Your brain doesn't like particles traveling up there. And the balloon, or the umbrella catches them. Then the umbrella, the stent is put in place, the umbrella is retrieved, the stent is left, and that's what you hopefully end up with.

And here is a stent being placed. The patient's arterial system is accessed in the groin, usually on the right side, because the surgeon here is right-handed, my colleague, Bob Hobson, vascular surgeon. And then everything is advanced up to the aorta, the aortic arch, into the carotid artery, and the procedure is then done. That's outside the brain where the arteries are muscular, and they are more resistant to manipulation by catheters and balloons.

And here is what a stenosis would look like before the stenting, and here is what the stenosis would look like after the stenting. We don't try to make the X-ray look perfect. The memory in the stent, which I mentioned earlier, the memory in the stent is to make the stent continue to expand. So you don't have to have a perfect result that day. And the stent holds back the clot. Now technology is working on, kind of we have an open cell system, closed cell system, hybrid systems, and of course, that's where technology comes back into the picture.

The results of this trial were published in the *New England Journal,* and they showed that carotid stenting and carotid endarterectomy were similar with regard to their safety. The big challenge though was to go inside the brain. And corkscrew devices were used, and failed. And then finally, a stent retriever device was used. And you can imagine the engineering that goes into something like this.

Here's the catheter. This all retracts back into the catheter, and then ends up like this, and then grabs onto the clot and can pull the clot out. And this has been a big advance in, basically, getting the clot. tPA, when it comes to big clots, can't really do the job. Now even though it's 2,000 times the concentration of endogenous tPA, you can imagine that clot that you saw right at the beginning, there really is only, there really only two avenues at that clot-- the proximal end and the distal end. And with big clots, intravenous tPA is just not adequately effective.

And here's what the clot would look like at the beginning of the procedure. And this is during the procedure. And this is at the end of the procedure. Now it's one thing to make a pretty angiogram, or to dissolve a clot, but remember our enemy of time, because time, that could be that intravenous tPA given an hour before this endovascular approach, that that time advantage could cancel out any advantage that the stent retriever device has. And so randomized trials had to be done.

And the first randomized trial, a large randomized trial, was only published a month ago. It was called Mr. Clean. It's a randomized trial, intention to treat design. The patient had to have demonstrated an occlusion of an artery within the brain involving the anterior circulation of the brain. So those would be the vessels coming off the two carotid arteries. The endpoints were blinded. You know, you can't blind the patient. They're going to know what happened. And the primary outcome was a score on a disability scale.

And without going into too much detail, this disability scale, zero means your normal, one means you're almost normal, two means you have mild disability, three means you're disabled, four means you're disabled and you can't carry out activities of daily living, five means you're, really, nursing home, and six, of course, you didn't make it. First of all, you can see that stroke is not a good thing to have. If you have an intracranial occlusion, your odds of dying are about 20%. And as I mentioned at the outset, stroke is the number four killer in the United States.

Let's look at the other end. No symptoms, again, you can see that the endovascular intervention, OK, it's much better. It's much better. But only 3% of the patients finished with no symptoms. You can see that in terms of very minor deficit or no symptoms, you've got 12% of the patients versus 6% of the patients. Going to the next grade, 21% versus 13%. And you could see for these areas that are, basically, better outcomes, there is a big difference between the two groups, which was statistically significant.

Nonetheless, we have a long way to go. The average time get this done was four hours. And one of the big challenges is to be able to do this as fast as the cardiologists do it. If you have an ST elevation MI today in Rochester, and you get to an emergency department in Rochester, and you're not in the cath lab and they're not at the clot within 60 minutes of when you arrive, that's not, that's considered poor medicine. And we really need to move here.

So while this device, this stent retriever will be licensed in the United States-- it's not yet licensed. It will be adjudged, I believe by the FDA panel. I have some experience with that. It will be adjudged as safe and effective, which is required for devices, but you can see that there really is much to be done to improve the outcome of these patients.

Now these patients were interviewed at 90 days after they had the procedure, and their families, over the telephone. And when I saw that reading the article, I said, uh oh. Because patients, when we were doing tPA, we would go by the next day and the patients this was when it was randomized and blinded. I didn't know who was getting it, OK? If the patient improved, the family, of course, said, boy, that tPA, isn't that tPA great? It's just wonderful stuff. And of course, could have been placebo.

The patients also, when they get something done, in general, there are exceptions, but they want to do better. So now here are these patients, they're in a big study, and they underwent this endovascular procedure with the stent retriever, they're in the cath lab. It's pretty dramatic. And then they call up at 90 days and try to go through this disability scale to see how well they're doing, and you can see the opportunities for bias. And so if that had been the only outcome of this trial, I would have been very skeptical.

But this is a look-- and by the way, it needs to be, it needs to be-- the FDA almost always requires two randomized trials. And I think they will require it in this case. But this is the volume of the CT scan in ccs. And you can see the intervention, 49 ccs, and the control group, 79 ccs in terms of the final infarct volume.

And look at that again, OK? If you measure the brain in a trial, which we did, the volume that you get measuring the brain in elderly patients is over 1,000 ccs on average. And remember, I showed you before that 20% of these patients died. And yet, how big really is 49 ccs? A tablespoon. I wonder how many of how many ccs in a tablespoon. A tablespoon is 15 ccs. That's it. 15 ccs.

So you're talking about a stroke in the intervention group and you saw that they had a lot of disability, they had 20% mortality, that by in average, 49 ccs. Is there an object that comes close to that? A golf ball is 43 ccs. So something the size of the golf ball, a little bigger, a little smaller, causes great disability and often causes death. So we have to do something about stroke. And this is just the article in the *New England Journal* that just came out.

Well, where do we stand here at Mayo Clinic with regard to technology? In terms of INDs and IDEs, Mayo is number three in the country, which I think is great. When I was at University of Chicago, believe it or not, as a medical student, I was advised, well, don't go up to Mayo Clinic. They don't do any research up there. Believe it or not, I was told that. And in here we are.

And this is just the Noncancer Center INDs. And Carol Durst, I thank her for these numbers. And the IDEs, you can see in the Noncancer Center, 89 and 12, that ranked number three in the country. And the cancer center has 104 INDs.

At Mayo, there's an office of regulatory research, regulatory support, which you can look up on the web page. And their common services include assistants with IND submissions to the FDA, FDA audit coordination and assistance-- and Carol, if you're listening, I haven't given up getting your help for CREST-2-- education and training, and then monitoring, which can be very expensive. NIH trials don't require monitoring. Good clinical trials have monitoring, but the FDA has another level of monitoring.

So for instance, in the CREST trial where we compared stenting to surgery, we had 117 clinical centers. And you can imagine how difficult it is to oversee the quality of the data at 117 different centers. One of the centers we discovered was actually manufacturing data. And it went to OHRP. They had to be removed from the study.

And remember, FDA is making decisions on what ends up in the pharmacy here, what ends up in the cath lab here, what ends up in radiology, and they have to get it right. And so as a result, we have to go out and audit, source document audit in FDA studies to make sure that the patient has properly consented, that the data that's in the case report forms can be documented in the medical record, that what happens, what we're told happens in our case report forms and the OR actually happened, because we have a responsibility to get it right so that we have appropriate drugs and devices.

So monitoring's important and expensive. We have a bid out for a grant that I'm involved in now, and the first bid we have for monitoring of 2,480 patients is over $4 million. $700,000 a year to monitor this particular grant.

So take home lessons. The basic sciences, including the most basic, continue as the fundamental contributors to 21st century medical care. tPA is one of the fastest drugs ever to make it to Walgreens. It was manufactured for the first time in human quantities in the early 1980s, and it was licensed for stroke in 1996, and licensed for MI in 1986. Remarkably fast. Remarkably fast. But it actually goes back to 1947, as I hope I've shown you. And it was physics, chemistry, electronics, and engineering. Engineers, chemical, electrical, metallurgical, are key players in translating science to human use.

When I started my own career, the neurosurgeon at our place, John Tew, who was President of the Neurosurgical Society at one point, he brought this point home, which I'm trying to convey to you today, and which we tried to do, carry out in Florida, and that is that our brains will not grow. In fact, as we mature, our brains will become more compact.

But technology, he said at the time, and I really took him seriously, technology is where you can make gains in your own particular research career. In Florida, during my eight years as Dean, I did everything I could-- and I think Sundeep knew a little bit about this-- I did everything I could with regard to our capital budget because it was our capital budget and the equipment that we were able to provide our investigators-- of course, you want the best investigators. But given the kind of the team that you've got, you've got to make sure that they are equipped with the very latest, best technology that you can give them.

You can just imagine when we started all of this work, laptops hadn't been invented. Nobody even thought about the internet, and that's only 30 years ago. Just imagine what it's going to be like 30 years from today.

Anyway, I am from Florida, and here some pipes. And my goal, of course, is to keep the pipes open. You do that with acute therapy such as this-- you remember that little figure with the alligator chopping away that I didn't go through in detail? This is actually the real thing. And anyway, it's been a delight to be here.

Today I can tell you that we're working on prevention as hard as we can. I didn't go into that today. Stroke treatment needs to get better. But the best way to treat stroke, of course, is to prevent it. So it's a delight to be in Rochester, and thanks very much for the turnout, and thanks for your attention. And if you have any questions, I'd be glad to try to answer them. Thank you very much.