Transcript of meeting: Saturday, June 15, 2019

This is an edited version of the transcription projected on the screen during the meeting. The transcriber used the "TypeWell" method synthesizing the essence of the discussion using advanced abbreviated software. Thus, the following is not necessarily verbatim.

Pam Spencer, Chapter Programs Chair: It is my pleasure to introduce Dr. Jay Rubinstein. He is a surgeon at University of Washington Medicine's Head and Neck Surgery Center, Director of the Bloedel Hearing Research Center, and a UW professor of Head and Neck Surgery and Bioengineering.

Dr. Rubinstein earned his M.D. and Ph.D. at University of Washington. His clinical interests include tumors of the lateral skull/face and rare disorders. He was president of the American Auditory Society. He has accomplished over 110 peer reviewed articles. Dr. Rubinstein has amazing capacity. His laboratory is working to develop an implant to help with balance disorders.

Welcome and thank you for coming up here.

Dr. Jay Rubinstein: Thank you. I like this horseshoe arrangement, much better than a classroom of desks.

I was asked to talk about hearing health possibilities for our great grandchildren's children. I scratched my head. That's a long time from now. I can't predict what is going to happen five years from now. But I thought about 120 years from now.

I generated this slide when I was in the Netherlands on sabbatical. You can tell it is from about 2004 because of the nature of the computer screen and image.

So, this is Rembrandt. He painted this in 1623. It is almost 400 years old. In that you can see -- this is called the Anatomy Lesson of Dr. Tulp. The cadaver was a famous criminal who had been executed. Dr. Tulp was a

renowned teacher of anatomy. He is demonstrating the anatomy of the forearm muscles.

He is working from a textbook you can't see but it is one of the first widely used textbooks of anatomy. The actual book in this painting, the original book still exists in a museum in Liden in the Netherlands. You can actually go to the library there is page through the copy of Vesalius that is in this painting.

But the point is that this is from almost 400 years ago. We still teach anatomy like this. We try to use computers but really you can't learn surgery without working with cadavers. We still do that today exactly the way it was done in 1623. So that is practically 400 years ago. I am only talking about 120 years from today, so my job is really easy.

Other things go back even further. This is a 2000-year-old sculpture in the Metropolitan Museum in NYC. This demonstrates an ear problem common to wrestlers. If you look at the ear, that is cauliflower ear. This is such a common injury that when I was on faculty at University of Iowa we trained coaches to drain the hematoma that cause this. When you get fluid in this part of the year you have about 48 hours to drain that liquid or you get the deformity shown in this sculpture.

So that everyone is on the same page I want to go over this page about hearing loss.

We will start with how it occurs, what we currently do to treat it and focus on the future, 120 years.

We start with the external ear. Why do we have an oracle? It is not just a place to keep your glasses or to hang your hearing aid. It is not decorative. It serves an important role. When we localize where sounds are coming from, we use our two years to tell horizontally where it is coming from. But we can't tell whether is in front or behind, but the oracle does. Two ears, without the oracle, you can't tell which angle it is coming from. This is a very important part of the ear even though we don't think about it a lot.

When we talk about the differences between a processor that sits on your ear, in your ear, or the back of your head for cochlear implants this is all something to keep in mind.

This is a normal ear drum. This is healthy. As you know, sound comes in and vibrates the ear drum, then it vibrates the hearing bones and they send vibrations to the cochlea which convert it to electrical discharges which go to the auditory nerve. The cochlea itself is spirally shaped. The word cochlea is Latin for snail. Many shells in nature are shaped in this way. The cochlea follows a very specific mathematical shape. Many shells follow this as well

The cochlea divides sound into frequencies. The cochlea itself has different chambers within it. Here is a cross section. These two compartments are called the scale of the stubli and tibuli. They have different colors because they have different chemical compositions. This is rich in potassium; these are rich in sodium. The chemical difference creates a battery. The cochlea has its own battery which increases the sensitivity to soft sounds.

There is a type of age-related hearing loss where the battery runs down. This is streal atrophy. The strea creates the chemical difference. If it is not working well the voltage of the battery starts to drop. When the voltage drops the sensitivity declines. But the clarity of the hearing is not changed. If you have a hearing aid and don't complain about how lousy it sounds, you have this type of hearing loss.

Basically, the batteries in the hearing aid replace the cochlea's natural battery. But this is about 10% of people with age related hearing loss. For most people hearing aids are effective but not ideal because they don't restore clarity. Most hearing loss is associated with loss of clarity because the other structures of the cochlea aren't working.

The hair cells that covert mechanical vibrations into electrical discharge connect here and connect to the brain. When these cells don't work, we put in a cochlear implant to stimulate the cochlea and bypass the structures seen here.

There are lots of types of hearing loss. Most people are aware of sensory neural hearing loss. We divide this in to three kinds. We have conductive, sensory and nerve hearing loss. We divide these because the treatments are different for each of these.

Here is an example of a person with a conductive hearing loss. This is a ball of wax obstructing the canal. Now you see the drum behind the wax and the sound can't get there. You can simulate a conductive hearing loss by sticking your finger in your ear. It blocks the sound.

There are other things that cause this. This is a person with a hole in their ear drum. It is a perforated ear drum. There is also calcification because of repeated infections. Sound vibrations can't vibrate the ear drum properly because it is not intact. The sound energy goes through the hole rather than vibrating the drum.

What causes sensory hearing loss? There is a list of things. This occurs because of a problem with the hair cells or problems like the battery in the cochlea I was telling you about. Anything that prevents the cochlea from converting mechanical vibrations to electrical discharges causes sensory hearing loss. Noise or head injury are common causes. Ototoxicity is something I will talk about in a minute.

A common antibiotic is called aminoglycosides and a very common one is hard on the kidneys. But it is effective against bacteria that infect bones. If you have a choice of dying of infection or going deaf, you usually choose going deaf.

Also, a common chemotherapy uses platinum which is toxic to hair cells and nerves.

There are over 140 genes that cause hearing loss. Generally, we are considered with genetically determined hearing loss in kids. Kids come in and demonstrate they can't hear. We can try to make them understand speech, but parents want to know why they are deaf. About half the time we can explain why, and it is about a quarter of the time due to genetics.

Some genes affect adults more than kids. These are genes that cause delayed onset hearing loss. Sometimes there is overlap. I have adult patients who have genetic defects that affect younger patients. But we don't know why it impacts some children and some adults differently.

All of what we call presbycusis has more to do with genetics than age. We can't differentiate a 30-year-old with progressive hearing loss and a 70-year-old with progressive hearing loss. One difference in 120 years, they won't say it looks like age related hearing loss, you will have a genetic test that immediately defines that. Or you will know as a baby that you will have hearing loss at 32 years old.

Right now, we can't predict when hearing loss will occur. Some genes cause deafness at birth, some take 30 years. We haven't made the connection yet but in 120 we will be able to put that together.

Meniere's disease, meningitis and auto immune diseases can all cause sensory hearing loss.

Nerve hearing loss. I am differentiating sensory and nerve hearing loss. Nerve affects the cochlear nerve itself. Noise exposure can affect the nerve without the hair cells. We used to believe that it was all caused by damages to the hairs. You have seen pictures of this I am sure. Our belief was that if someone had noise induced hearing loss the hairs would be damaged and then the nerves would degenerate.

Recent research demonstrates that noise can be toxic to the hearing nerve itself. Some levels can cause loss without damaging the hairs. One scientist at our center has a grant to develop tests that will allow us to determine if someone has hearing loss due to this mechanism.

There are also genes that code for nerve defenses or atrophy of the cochlear nerve. Meningitis can affect the nerve as it enters the brain. Also, tumors of the skull base can involve the auditory nerve. Here is an example of someone with a disease that causes bilateral acoustic neuromas. This is the brain stem being squeezed between tumors. It is amazing to see someone coming in with this and only having some tinnitus and hearing

loss but feel fine otherwise.

One of the things that we hope to make better in 120 years is dealing with this.

So how to deal with this. Noise protection and head protection. A younger person coming in with complete deafness in one ear due to a virus is common. People want to know how to protect the other ear - do simple things like wearing a helmet when riding a bike. Head protection is important. When people are being treated with medications like I told you about, we now routinely monitor their hearing when we can.

Lots of people undergoing cancer chemotherapy can be monitored. Sometimes the oncologist will lessen doses of chemotherapy to protect the hearing. The third thing is something that our great grandchildren's children may have medicine to prevent this. I will talk about this more in a minute.

As everyone knows there are a number of ways to treat hearing loss. If there is fluid behind the ear drum, we take it out. We do this with children all the time.

With good speech discrimination we observe and use hearing aids. We are hoping that we can increase the uptake of this in our population. With moderate speech discrimination we observe, hearing aids and also hybrid or electroacoustic cochlear implants.

When people have poor speech discrimination, we use a cochlear implant, either on one side or bilateral. This is an electrode those goes into the cochlea with an electro stimulator that goes under the skin. This is old picture. People used to have a cable that went down their neck and attached to a reader on the belt. I have been doing these since 1994 and people used to all have these on their belt like we now have phones.

If you go back a couple years sooner, the smallest speech processor fit in a briefcase. A professor at University of Washington was at Stanford in grad school and his Ph.D. was about building a multi-channel speech processor. Mannel was founded by people at Stanford as well. The idea for this

processor was that if you have a choice between being deaf and carrying a briefcase to hear, people would prefer the briefcase. But to see what gets squeezed into something on the back of the head is incredible to me.

We have the cochlear device, the Advanced Bionics and Med-El devices. There are others we haven't approved yet but there are two in China. I have implanted a nucleus device in Shanghai. It was essentially like putting one in years ago. There is also an Indian company and a Korean company that produce these. The last one you will probably be aware of soon is Oticon, which purchased a French cochlear company called Neurelec SA. I know that they are seeking FDA approva. Soon there will be four devices on the market in the US.

Pictures you are familiar with. The cochlear device, the Advanced Bionics, the Med-El. I love this picture because when I first saw it, I was floored. There were a couple of experiences that amazed me in my career. When I was first involved in cochlear implants, I was at a center in Boston that only did adults. In Iowa Dr. Gatz had done the first pediatric implant in the U.S., a three-year-old. he called his name and the child turned around and said, "What?" This was a congenitally deaf child who learned to speak a receiving a cochlear implant.

The second thing was when I first saw this image, I did this surgery and at this point we saved hearing with these implants but having a cochlear implant and a hearing aid was foreign to us. Now it is more common.

So other things that our great grandchildren's children will benefit from. This is an image of our first-generation vestibular implant. We went to all the implant companies and asked them to manufacture this. It seems simple but this is 150 microns in diameter. This is 3x smaller than the smallest cochlear implant. We put a request in for this design.

We wanted such a small array to go in the semicircular canal to help with balance. There are three balance canals in the ear to tell you where your head is going. Each of these arrays goes in to one of those. This was our first human subject back in 2010. We implanted 10 monkeys at University of Washington with this same device and this was the first time we brought

him in for testing.

His T-shirt says, "Monkey Boy 11." When we first turned this on nothing happened. We started at a low level. As we increased the current, he said he was being rotated 30 ° to the right. We turned it up and he said he was 45 ° to the right. This was the first human experiment with a device that provides movement sensitivity to the brain.

We implanted four people with that device. We had a lot of problems and redesigned it. This is our newer device which combines a balance prothesis and a cochlear implant. We have put this in to three people. Here are two of them. They wear an accelerometer on their head. If you have fooled around with a phone, when you turn a phone its side and switches from portrait to landscape, that is why.

Twenty years ago, accelerometers cost $100,000 a piece. Now they are about 10 cents. Do you have a Baja? When your head turns, it measures the rotation of the head. It provides that information through the electronics here. Here they are moving around the lab with their devices.

This gentleman has an Advanced Bionics cochlear implant in one ear and a balance prosthesis with a hearing aid in the other. She has a cochlear and stimulator and then a hearing aid.

There are three centers in the world doing research. We at UW Bloedel are doing it, Johns Hopkins, then a European group combining Spain, Geneva and others are working on this. We will see this sooner than our great grandchildren's children. It will help people with balance disorders.

What is the big thing we want to do in the future? The biggest thing is to prevent age related hearing loss. Other things we can do is reduce noise induced. It is very hard to avoid noise and is varied how much noise affects you.

Prevention and treatment of genetic hearing loss. Some disorders produce deafness. There have been animals who have an analogous deficit to deaf kids and have be cured through gene therapy. This is a very specific case.

We tried to recruit him, but Boston kept him. The gene this individual is studying is in TMC gene. This encodes the protein in hair cells that is responsible for the voltage change on the hair. This is a very important protein. Without TMC everyone would be deaf and would have no balance.

There is a rare human defect where you have no TMC gene. He created an animal model of TMC genetic defenses and was able to cure it with gene therapy. So, they have functioning hair cells and hearing.

This is incredibly rare in humans but is a terrific model for what the future holds. We can identify certain kinds of genetic defenses and treat it.

Prevention is another interesting area. We have a good model for how to develop preventative drugs. Ed Rubel discovered birds regenerate their hair cells. He has gotten out of the regeneration field. but others have taken it up. He has taken up a mechanism for screening drugs for their toxicity to the ear and their ability to protect the ear. They have developed a new drug called ORC13661.

The goal here was preventing hearing loss due to antibiotics. What they did was take a zebra fish which is a commonly used model for the year. These are tiny so you can study thousands at a time. They reproduce quickly. They all have these organs which are literal line organs. These are like a cochlea, but they sense vibration in the water. They can test fish behavior by making them swim away. It is an escape reflex. These hair cells are right on the surface. They can study these very easily.

These are green because they have been labeled with a green dye. These are live fish and live hair cells. These are sitting on the surface. They can do stuff like mix the fish with amino glycoside. They can test drugs to see if it might protect the fish. When they find one that protects the fish, well the first is proto 1. They teamed up with a medicinal chemist and made a more potent version. This is the drug I told you about.

First in fish and then in rats and now even in people they are proving the prevention of hearing loss. These are different frequencies. Rats hear up to 32 Hertz. This is the measurement of hearing with the drug. If you give

them the drug and the amino glycoside, we see the results here.

As they increase the dose of the ORC, the amount of hearing loss goes down. This is extremely protective. It has gone through Phase One FDA trials. They are designing Phase Two right now. This was sold to a drug company which is going to be running that trial.

Other tests show it didn't inhabit the antibacterial aspect of the antibiotic. This was very important.

What makes this stuff exciting for our great grandchildren's children is that hair cells have a very limited repertoire of how they die. The mechanisms by which they die are limited. There is good reason to believe that drugs like this, if not this specific drug, will not only prevent hair cell death from amino glycoside. There are many things that cause hair cells to die that can be stopped with the same strategy. We might have a pill we can give people. We can identify them genetically at a young age and give them a pill to prevent it.

We go through all these efforts to treat hearing loss but now we might be able to prevent it.

None of this will happen tomorrow but this is all being done in labs right now. The stuff happening tomorrow is stuff like I usually talk about. Improved devices, improved applications of existing devices. We already have levels of speech understanding that I couldn't imagine at the beginning of my career. I started researching cochlea in 1984 and restoring speech was a fantasy. The belief was it would never work. When we proved it worked, it was an improvement of 10%. Now we have 60%.

Timmy, who I talked about before, he is now close to 40 and has a master's in bioengineering from university of Iowa and works in medical device field. He was born in an era where deaf children often ended up with a fourth-grade education.

There is considerable interest in aging and hearing loss. There have recently been many discoveries between hearing and cognitive impairment. Two-

thirds of adults over 70 have significant hearing loss. Hearing impairment in older adults has a 30-40% acceleration of cognitive decline. But does treating hearing loss prevent dementia? There are good reasons to think it might and good reasons to think it might not.

Loss of smell is also associated with cognitive decline. These might all represent different types of brain aging. But this is an active area of research right now. Our great grandchildren's children will know the relationship between hearing loss and cognitive decline.

OK, I am pretty much out of time. I will stop here and answer questions.

[Applause]

Vicki: I have a Baja on this side. Single sided defenses. Early on in your talk you showed a picture of potassium and sodium, that powers the stria. Is it possible to -- that can be bad? Or the cochlea. How do you determine which has gone bad?

Dr. Jay Rubinstein: Most forms of hearing loss use multiple mechanisms. The best test we have is the regular behavioral audio graph. If someone comes in with 50% loss with normal speech recognition it means one thing. If someone has normal hearing to 2000 Hertz but high loss above that, it is probably hair cell loss. If people have sloping and poor speech discrimination it is probably neural.

All these individuals probably have a combination of all with one predominant loss.

Vicki: So, when I go for a complete assessment is that part of the -- if they can determine -- will it be treated differently?

Dr. Jay Rubinstein: Well fundamentally it doesn't change what one does. I am an academic so I go into that level of detail but most won't do that and might not be aware of some classifications. It doesn't fundamentally change what you do. I am trying to dream up ways to affect our great grandchildren's children. I worry about that level of detail and share it with

my patients, but it doesn't practically affect the patients.

Speaker: I have read an article where they identified genes associated with hearing loss. Is there a way to improve hair cells?

Dr. Jay Rubinstein: These are two things. People with genetic defenses - we want to reverse that. We want to fix the copy of their gene. But gene therapy can also be used to treat non genetic hearing loss. For example, if someone has noise induced hearing loss, we want to regenerate their hair cells. There are three potential ways to do that. We can potentially give a drug that makes the other cells in the cochlea turn in to hair cells. That's one possibility.

We can do gene therapy to turn them into hair cells. Or we can potentially implant stem cells that grow into hair cells. Those are strategies being studied. Gene therapy holds promise as a tool for regeneration and as a cure for forms of deafness.

There are about 140 genes identified that cause hearing loss. We are excited about this because one of the leaders in genome sciences has recently become interested in the genetics of hearing loss. One of her graduate students works with me at Childrens Hospital. We might move that into the adult clinic to test everyone for the genetics. We are studying kids now. If you are doing a genetic clinic in children, you'll find about 25% have genetic problems but with adults it is only about 10%.

Historically we looked at blood tests, but Dr. King is using saliva. It is easier to get kids to spit than to get them to draw blood.

Don: I read recently about a doctor in South Africa who made bones in the ear with a 3D printer. Do you think that has a future in your work?

Dr. Jay Rubinstein: Yes. They have been used to create ear drums as well as models of the inner ear for surgeons to practice on. But the problem with generating hearing bones is the same problem we have with using prosthetic hearing bones and that is the material it is made of. Even the most biocompatible materials are not perfect. They cause reactions and the

ear recognizes this is not a natural structure. If we come up with material to 3D print, we have a much more viable option.

If I can pull up the CT scan for a patient and print a custom piece to use right then, that would be great. Currently I measure the distance I am trying to close the gap and I take a prosthetic hearing bone and trim it. All of that could be eliminated and that would get rid of a lot of guess work. But we need a material to print with. This is always a challenge. There are lots of applications in 3D printing for kids born without an ear. But that is going to be available in the next generation.

Jerry Finkbonner: I have a concern. Most humans in their teens, 20's and 30's think they are invincible. But recently in the last generation or two you see so many wearing headsets and music blaring where you can hear it outside. The motorcycles and cars with loud engines. For most of us age is the big issue but what prediction can you make for future generations who have increased the potential for noise induced hearing loss.

That potential exists. We have devices that are much more flexible to listen to music 24 hours a day at high levels. There is a lot of concern that this will cause an epidemic of noise induced hearing loss. But the same concerns were brought when the Sony Walkman was introduced. This was actually before I was in medicine, but it was the first truly portable music source. A Walkman could only do a cassette tape which is 45 minutes a side. Then you'd have to switch. But in the time it took to switch them out you would get a break. Now you get no break. People can listen to music nonstop.

The larger concern is the greater loudness and the ease with which people can listen to it. If someone is listening to music in a headset loud enough for others to hear, that is too loud. Most people know that. The problem is wearing your earphones while walking around. Maybe a construction project is making 80 decibels, so you turn it up your music to 120 decibels. That is really the concern. It is so ubiquitous and there is no break.

We have not seen this epidemic yet, so we don't know about the practical effect. But in the field, we wonder about it. It isn't the earbuds; it is the level of sound and duration of exposure. Hearing loss is caused by

amplitude and duration. High amplitude for short time, not a big deal. Low amplitude for long times, not a big deal. High amplitude for long times, we are concerned.

Charlene: Thank you Dr. Rubinstein. You implanted me 10 years ago. You are not the only one in here you have helped. Bert came in three months before me and I waited until he was okay before I went in. As concerned as we are for the generations ahead, I want everyone in here to know how much we with cochlear implants have regained and celebrated the quality of our lives.

Dr. Jay Rubinstein: That has been the best part of being in this field. Getting to observe this change. When I started cochlear implants were an experiment. We never thought it would be commonplace.

I was at a conference years ago. There was a strike and I was watching the news where the CEO of Cochlear talked about why people were on strike. I was stunned that this thing I studied for so long was something where workers can actually go on strike. It is mind boggling to me! The reason is that because of the impact it has on people. Older adults and kids born deaf. Everyone has an extraordinary experience. I am very privileged.

Pam Spencer: What about genetic testing?

Dr. Jay Rubinstein: There is currently a research study and a commercial product. Otoscope costs about $1,200 to run and most insurance does not cover it. Some does. I have never successfully gotten an adult authorized.

We are going to be able to get genetic testing with everyone. Dr. King's lab will piggyback on this along with their routine research. We are hoping to test adults as well.

Pam Spencer: The other thing I want to share is that the my audiology clinic has donated $10,000 to the Bloedel research center. I want to continue to donate to the research that is going on because it is leading edge. I want to give back to my future grandchildren.

Joan Baker: I have genetic hearing loss. Two grandparents were almost totally deaf. They passed away in the 50s. I have five siblings and only one other than me has hearing loss. I am the only one who had hearing loss at a young age, early adulthood. The other sibling's hearing loss is age related. How can genetic testing be done in this case to find if mine was genetically induced when everyone else who had the hearing loss is dead.

Dr. Jay Rubinstein: Gene discovery, which is the process of discovering new genes, requires multiple generations and multiple family members. If you have a known gene that produces this loss, then you don't need family members. It is just you. So, if we are searching the known genes, we can tell you that such and such gene is causing such and such loss.

I have two patients who are siblings at Seattle Childrens who have the same genetic deafness. Now they both have cochlear implants. The loss in their other ears has been very different. The fact that your siblings' loss is different than yours is not very surprising. You might both have genetic hearing losses. You might have a gene where the manifestation is highly variable. That is part of the understanding. We know a lot of genes that cause the loss, but we know little about what hearing loss that causes.

For example. we want to know why a child will do well with a cochlear implant and another won't. We want to know that up front, but we currently have no way of knowing. We don't have the correlation between the genetic cause and the clinical issue. That is the research that will occur over the next 50 years.

Joanne Boschman: I have genetic hearing loss. It went through the family for generations. Some children have completely normal hearing and others have a loss. We had one child with hearing loss. We adopted our other two children to prevent having more children with hearing loss. Our son has two boys with normal hearing. I am Canadian and I got a cochlear implant and was very nervous, but you said the same thing. It is hard to tell how it will work and it has worked majestically well. From when it turned on, I have heard wonderfully. I had get used to the background noise I had been going along with years without doing anything because I was nervous.

When I was tested eight years ago, they told me I could have the cochlear in my left ear. When I went to Pam Spencer, she said to tell them to do the right ear. The left ear had better hearing and my understanding was better in my right. It has worked so well.

Dr. Jay Rubinstein: That is wonderful. The story of generations skipping hearing loss. Most genetic forms can skip. Even two deaf parents can often have a hearing child. It doesn't necessarily hold through every generation.

Pam Spencer: Thank you so very much, Dr. Rubinstein. That was most informative. We appreciate the effort you made to come up and we all enjoyed your presentation.

Larry Wonnacott: That was fantastic. Thank you so much.

Dr. Jay Rubinstein: Have a great day!