ANA2022 MEDIA ROUNDTABLE TRANSCRIPT

Near the close of its 147th Annual Meeting, which took place in Chicago October 22–25, 2022, the American Neurological Association held a Media Roundtable to allow members of the press to hear about the cutting-edge science presented at the meeting and connect with leading academic neurologists and neuroscientists. The Roundtable took place October 25 at 11 a.m. U.S. Central time. Presenters included:

- ANA President Frances E. Jensen, MD, FACP, FANA (University of Pennsylvania), highlighting the Presidential Symposium "Neurologic Dark Matter: Exploring the Exposome that Drives Neurological Disorders" and the plenary session "Emerging Role of Somatic Mutations in Neurology".
- Roy H. Hamilton, MD, MS, FANA (University of Pennsylvania), highlighting the closing plenary, "Advancing Neurologic Equity: Challenges and Paths Forward."
- Krishnankutty Sathian, MBBS, PhD, FANA (Pennsylvania State University), discussing the "Novel Perspectives on Neurodegeneration" session.
- Jack M. Parent, MD, FANA (University of Michigan), discussing the meeting's opening session, "Brain Organoid Models of Neurological Disorders."

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TRANSCRIPT FOLLOWS

Dr. Frances Jensen, Introduction
Hi, I'm Dr. Frances Jensen and I am the president of the ANA. We are delighted to have the opportunity to share with you some of the concepts that have come out of this meeting. Just a quick word about the ANA. It's the American Neurological Association, and it's actually an association for the field of academic neurologists — thought leaders in the field, and many trainees and people who are doing sort of the cutting edge, groundbreaking work that has to require an academic setting, university or health care system to occur. This includes innovations in research, in training, in clinical firsts — first-in-human trials actually to implement a brand new cutting-edge therapy — in population health and also global health initiatives.

So we covered a lot of those at our meeting. We've selected our plenaries to discuss today, although there may be other things in the special interest groups that are interesting to you, and if so, you can certainly come back to us, and we can connect you with those people because they are not present at our meeting. But right now what you are going to hear are the major academic symposia plenaries that were presented, which generally represent a future-forward look at our field in anticipation of where the field of neurology is going — the fastest moving area of biomedicine in all of medicine. Right now, where the changes that have happened in the last five years in our practices include reversing strokes, application of laser therapy for diseases like epilepsy, new immunosuppressants that never existed before, for things like multiple sclerosis, and also gene therapy where we're actually changing the genes of a person to cure their disease. Since so many of our brain diseases are genetic in nature, these are just a sampling of the kinds of things that we are in a revolution right now in our field. It's a very exciting time.

So with no further ado I'm going to hand you over to Dr. Jack Parent, who's going to describe his symposium. Then we will sequentially go through the six symposia! And each of the chair people will introduce themselves, and we will take questions at the end.

Jack Parent, "Brain Organoid Models of Neurological Disorders"
Hello, everybody. My name is Jack Parent from the University of Michigan. I chaired the brain organoid symposium. It was the first plenary session of the meeting, and it was on the topic of using brain organoids to model neurological disease.

So, brain organoids are a cutting-edge technique to take human pluripotent stem cells — either induce pluripotent stem cells or embryonic stem cells derived from patient skin or blood cells — and culture them in three dimensions to form brain-like structures that self-organize and you can apply patterning factors to get specific brain regions that develop in culture.

So we now, through this technique, have the ability to look at the earliest stages of human brain development, and also using genetically modified organoids or organoids from patients with mutations, look at how diseases develop and manifest in human cultured cells.

So Arnold Kriegstein gave the first talk. He described the uses of organoids, they can be patterned in the cerebral cortex into other brain regions like hippocampus, thalamus, spinal cord, and then they can be combined into fusion, or assembloids, where there are two different brain regions that are connected. He has been using organoids to study malformations of cortical development, and he talked about lissencephaly, or smooth brain, which is a severe malformation of cortical development where the gyri and sulci, the folds of the brain, don't form, and by studying brain organoids derived from patients with lissencephaly he identified the cell types in the developing brain in the neural stem cell niche that were disrupted, including a cell type known as outer radial glia, which give rise to neurons in the superficial cortical layers.

He then described a really cool use of the organoid technique to look at evolution. So one doesn't have access to fetal chimpanzee brains or chimpanzee embryos or fetal human and

different types of primates. But using brain organoids grown from skin cells, for example, from chimpanzees that have been reprogrammed to stem cells, he could compare cell types and gene expression in human organoids, chimpanzee organoids, and he looked at both macaque organoids and fetal tissue, and he found cell types that were present in the human organoids that were not present in related primate species, and similarly different gene expression profiles, and a lot of these are part of the early stem cells that give rise to the outer cortical layers and the expansion of the human brain.
So I think it's a really novel use of this approach.

The second talk was by M. Elizabeth Ross or Betsy Ross, who's a professor at Cornell. She's a human geneticist and neurologist who talked about the use of brain organoids to study microcephaly, which is a common cause of disability in children. It's a brain malformation where the brain is smaller and they have intellectual disability and developmental delay. She looked at specific gene mutations that cause microcephaly, including in the occludin gene, and found that they disrupt stem cell division in the organoids and caused the organoids to be smaller than isogenic control organoids modeling this microcephaly.

And then she described the use of brain organoids to study neural tube defects, which is a really novel and exciting application. So there's a new technique that actually was developed by my lab, and a scientist, Andrew Tidball, who now works in collaboration with Betsy to study how drugs can cause neural tube defects using these single rosette brain organoids. Where the structure is easily identified, and you can give, for example, valproic acid, which is, ah, an anti-seizure medication known to cause neural tube defects, and it caused, ah, changes in the organoids that weren't seen with derivatives that aren't known to be teratogenic or cause defects. Betsy is now using these to study spontaneous, families with spontaneous neural tube defects in multiple births, looking at combinations of genes that are likely to be affected.

The third talk was Ranmal Samarasinghe from UCLA using brain organoids to study network function in epilepsies. And so one can let the brain organoids mature. For four to five months they develop cortical layers, and he fuses excitatory and inhibitory organoids, because the interneurons in the brain, the inhibitory cells come from a different location than the excitatory cells. So when you fuse them, the interneurons migrate in and form networks, and he can record from them and show that they have rhythmic oscillations that are similar to the developing human brain, and when he makes organoids, these fusion organoids, from patients with genetic epilepsies he sees disruptions in these oscillations and the development of seizure-like activity in the organoid. He also modeled a hippocampus, and found deficits in rhythms associated with learning and memory in hippocampal organoids

The last talk was by Sally Temple, who used organoids to study neurodegenerative disease, and showed that mutant Tau causes glutamaturgic cell death, so excitatory neuron death in the organoids, and that she could determine the mechanism and block this by manipulating RNA binding proteins.

So that's our session in a nutshell.

Kris Sathian, “Novel Perspectives on Neurodegeneration”
Thanks, Jack. So my name is Kris Sathian: I'm at Penn State, and our symposium was on novel perspectives on neurodegeneration. What we tried to do in this symposium just overall was, try to take a step back and try to examine what might be some features that are common to the various neurogenetic disorders as opposed to the more typical focus where we are kind of down in the weeds of what's gone wrong with a specific disorder like Alzheimer's or Parkinson's, we’re really trying to take a step back and see what might be common.

So the first speaker was Julie Schneider from Rush University Medical Center, and she spoke about her work, showing that people who are clinically diagnosed in life as having Alzheimer's dementia, turn out on autopsy to really have multiple pathologies. She listed at least four different kinds of pathologies. One is a classic pathology of Alzheimer's disease that involves the misfolded proteins amyloid and tau; the second is vascular pathology; the third is pathology associated with Lewy bodies in the cortex, and the fourth is a recently described pathology, which has got a very long name. The full name is limbic-predominant age-related TDP-43 encephalopathy and the acronym for that is LATE, and it turns out that, for example, seventy-five percent of these patients actually have at least some vascular pathology. She also showed some very elegant modeling, showing that these multiple pathologies actually account for the association between age and dementia. So the idea that, you know we get the, the probability of dementia increases with age is accounted for by the fact that we have multiple pathologies accumulating with age. And as we have multiple pathologies that lowers the threshold for dementia, and she also showed that there are interactions between these multiple pathologies and causing dementia.

So let me move on to the second speaker. That was Rita Guerreiro from the Van Andel Institute, and she recounted her work on studies in a variety of multi-ethnic populations, including Turkish populations, Ashkenazi Jewish populations and people, in Portugal. And so this gives us a perspective that is a little bit different from traditional focus on specifically populations that are largely white, and what she showed is, she examined a couple of different genetic mutations, and showed that this kind of mutations in these genes can actually be represented by a variety of different phenotypes. For example, she showed that a mutation in the progranulin gene can be associated, not only with dementia associated with Lewy bodies, or Lewy body dementia, but also with the frontotemporal dementia. It can increase the risk for Alzheimer's and Parkinson's disease, and also in some cases cause the very early onset neurodegenerative disorder known as neuronal ceroid lipofuscinosis, or NCL. And she showed this in, in a couple of other examples as well

Moving on to the third talk, that was by David Holtzman from Washington University in St. Louis, and he focused on a protein, apolipoprotein e. Variations in the genes for this protein have been shown to be the strongest predictive risk factors for Alzheimer's disease in terms of increasing risk, as well as in terms of decreasing risk, depending on which variant an individual has. What he showed was that — and he used a variety of methods to show this in animal models and mouse models — he showed, using antisense oligonucleotides, as well as antibodies to amyloid

beta, the amyloid beta protein — oh, actually, to apolipoprotein e — that the apolipoprotein e is actually pathologically, pathophysiologically, involved in what we think of as the amyloid cascade. It's involved in the seeding of amyloid, it's involved in the amyloid-induced seeding and spread of tau, which is the protein that's deposited later in the stage of the disease, and it's also involved in microglial activation and subsequent neurodegeneration, and so made the case that this could be a very strong therapeutic target.

And the last talk was by Vassilis Koliatsos from Johns Hopkins University who focused on axonal degeneration, who used his studies on traumatic brain injury to examine the course of axonal degeneration, and how this might be a contributory factor, and pointed out that this may be also relevant to a number of other neurotransmitters.

Frances Jensen, "Neurologic Dark Matter: Exploring the Exposome that Drives Neurological Disorders"

Hi! I'm Frances Jensen and I'm going to talk about the Presidential Symposium, which was entitled Neurologic Dark Matter: Exploring the Exposome that Drives Neurological Disorders. And what does this really mean?

We want to take this opportunity to highlight a really important and completely under acknowledged or recognized issue, that neuro-contaminants — environmental contaminants — actually are having profound effects on the nervous system. When the public thinks of pollution, air pollution, water pollution, ground pollution, they think of asthma, lung disease, cancer. But what we're trying to is that the brain and the nervous system are possibly the most sensitive organ systems of lifelong accumulation of contacts with neuro-contaminants, be they in the air, the water, the ground, et cetera. So we call this the exposome. And this is a new, relatively new term for neurology and neuropsychiatry. But we felt that it was time for a wake-up call because there's a lot of new information right now that has come out around specific diseases.

So we started it with a discussion by Deborah Cory-Slechta from the University of Rochester, who is an advocate as well as a long-standing researcher in this area, and she spoke widely about chemical exposures as an ignored environmental risk factor for both diseases of the developing nervous system and diseases of the aging nervous system.

She points to the fact that we all do know about lead. That is one thing we know about is lead. But lead, as she, as she calls it, is a poster child for much more. There are so many other contaminants besides lead, and to think about, what is, what is our relationship as physicians and researchers with the EPA to sort of open their eyes as to some of the things that are going on. She talked about the fact that beyond lead there's been a lot of interest in agricultural pesticides like paraquat and Gramoxone, glyphosate which is Roundup, and that it's not just in the ground. These things actually become aerosolized, and they're in the air, and it is a time to be very concerned. There's also issues with ultra-fine particles and heavy metals, and that these have been related to diseases from neurodevelopmental disorders — we know the story with lead, obviously — but also neurodegenerative disorders like dementia, Lou Gehrig's disease (ALS) and Parkinson's disease. She did a nice introduction and I would refer you to her to

personally discuss this. She's been an advocate in the field for many, many years, she's phenomenal.

Devon Payne-Sturges, who came after her, from the University of Maryland, we wanted to get right up there: racial disparities in exposures to environmental contaminants. Guess who lives by the highways? Guess who lives in old smelting grounds? And also in old factory and pesticide-rich agricultural areas? You know. Lands that have been converted into, often, urban housing.

So she pointed out that there are now really well-known disparities in things like lead exposures that are higher among low-income and Black children. Higher ambient air pollution found in non-white and low-income communities. Children with households with lower incomes have significantly higher levels of some of these contaminants.

There are actual measures, for instance, on effects on IQ. That show Hispanic children living in agricultural communities exposed to these pesticides and social adversity, have lower, significantly lower IQ scores correlated with their exposure as well as issues in Black children shown with social responsiveness that's correlating with exposure to pesticides. Overall that low-income children exposed to air pollution have a, have significant issues with cognitive function and lower IQs. So she poised the pointed question: How many IQ points do we have to lose per person to do something about this? It was very profound, and I would refer you to her at the University of Maryland. She's an advocate, but also a bona fide outstanding researcher in this field.

The next person was Eva Feldman, who's from the University of Michigan, who is working on actually something that is particularly bad in the state of Michigan because of its manufacturing history, and also pesticides in the agricultural farmland.

She is specifically interested in ALS, Lou Gherig's disease, which, as you know, is a progressive and rapid loss of motor function, due to a specific toxicity to the motor neurons anywhere, in the spinal cord, but also in the brain. They can have a cognitive impairment as well, and these people become progressively paralyzed and pass usually within two years of the diagnosis.

She has been very interested in the fact that there are really remarkable clusters in neighborhoods, in many states. But she pointed to the ones in Michigan, and specifically in her talk she said that at this rate, ALS will be increased by 40% by 2040, which is an alarming number, because it used to be quite a rare disease.

And so speaking of rare diseases, other tools in our material are genes, and we can do, look at people's genetic backgrounds, and she showed that there are certain risk factors you can find in people that explain some of this.

Tim Greenamyre, who came next from the University of Pittsburgh talked about very basic science, looking at the effects of rotenone and trichloroethylene, which is a solvent for greases, oils and fats, and rotenone as in pesticides, really activating known pathways in Parkinson's

disease, and showing how this can actually happen, so really giving us some mechanism. It's known that Parkinson's disease is the fastest growing brain disease at this point in time and is likely to have a potential environmental factor to that.

The final speaker was Ray Dorsey, who gave a very colorful talk — worth looking at on the on the video of our session — "Is the rise in incidence of Parkinson's largely man-made?" um, and gives a big argument about paraquat and TCE, polychlor—PCBs, polychlorinated biphenyls, air pollution, and certain occupations like construction being associated with these diseases.

And so at the end, the moderators of this, I will just like to say, were Walter Koroshetz, Director of the National Institute of Neurological Disease, and Rick Woychik who is the Director of the National Institute of Environmental Health Sciences, showing that they're taking this very seriously. And these two groups are going together and suggesting we need a lot more research, so the session was a kind of a big wake-up call for our field.

Roy Hamilton, "Advancing Neurologic Equity: Challenges and Paths Forward"
My name is Roy Hamilton. I am a professor of neurology at the University of Pennsylvania, and also I am the Vice Chair for Inclusion and Diversity there. I'm reporting on this last plenary topic, which has the distinction of being the one plenary that hasn't actually happened yet. So I will be predicting the future in some of my comments about Advancing Health Equity: Challenges and Paths Forward.

So we know that many of our most common and burdensome neurologic diseases disproportionately affect persons belonging to marginalized groups. These individuals face many challenges that increase their likelihood over a range of neurologic disorders, impose barriers on their ability to access neurologic care, and give rise to inequities with respect to how they're treated when they seek care from health professionals. So addressing these kinds of barriers and disparities is critical to ensuring that excellent neurologic care is provided to an increasingly diverse population.

So in this symposium we'll have presenters discuss how racial and ethnic disparities impact two particular diagnoses, two particular neurologic disorders. That is, Alzheimer's disease and multiple sclerosis, and the symposium also address how neurological disorders impact the LGBTQ community, and how and why clinicians and researchers need to be attuned to environmental exposures and other exposures throughout the lifespan in individuals from marginalized, minoritized, and otherwise disadvantaged communities.

So to get into the individual talks, Monica Rivera Mindt from Fordham University will kick things off with a talk about disparities and inequity in Alzheimer's disease and related dementia, and research related to these disorders. Just to give you a couple of quick facts about that: compared to [non-Hispanic white] older adults, older Black and Latinx individuals may be up to three times as likely to be diagnosed with Alzheimer's disease or related dementias. If we continue with current demographic and age-related trends in the population, by 2030 Latinx and Black American families will comprise about 40% of the 8.4 million Americans who are affected

by Alzheimer's disease and related dementias, and compared to older non-Hispanic White adults, these same populations of individuals are 30%–40% less likely to seek neurologic care or to receive neurologic care for their diagnoses. And so her talk is going to highlight two critical ways our field can improve brain health equity by increasing the representation of minoritized populations in dementia studies, and how we have to use culturally informed and community engaged research methods and expanding our knowledge with respect to these social, cultural, and structural mechanisms. How often that affects the pathogenesis and treatment of Alzheimer's and related dimensions.

So then we'll transition to Lilyana Amezcua, who's at the Keck School of Medicine at USC. And she'll focus on disparities in multiple sclerosis. Now the received wisdom, you know, certainly, when I trained, the received wisdom was that multiple sclerosis was a disease of white persons, and, in fact, that you placed it lower on your differential diagnosis if a person was not white, and certainly evidence has demonstrated in recent years that that is anything but true, right, and that if these populations are as affected, and in particular individuals who are Black or African American, that they may be even more severely affected in terms of outcomes. And so her talk will review much of this data. But we'll also focus on the idea that investigations to date have, have largely focused on characterizing this disparity, we can intervene in some of the social determinants of health and other factors that lead to these kinds of disparities in multiple sclerosis and related disorders.

Nicole Rosendale from UCSF is going to tell us about the neurologic disorders and neurologic impact that is seen in individuals who are sexual orientation and gender identity minorities, and how important, how these important aspects of identity are relevant to health, and should be features that neurologists ought to be comfortable asking about and assessing, and she has been a leader in demonstrating that while neurologists may feel that that is the case, that, in fact, on the whole, they are not broadly prepared to address this important aspect of patients' histories. I mean, she'll present cases which demonstrate that there are important diagnoses, important things that can be missed. If a clinician is not aware of how to approach an individual with respect to their sexual orientation and their gender identity, and then we'll also highlight the need for individuals in the LGBTQ+ community to be able to feel comfortable seeking care and care that touches on their identities as individuals with respect to their sexual orientation and gender identity, and how that, that makes it incumbent on neurologists to be knowledgeable about these things.

We'll wrap up our invited faculty speakers with Amy Kind, who is a real pioneer in capturing and quantifying the manner and degree in which the place one is situated, and the environment in which one lives, exposes one to, to different health impacts and health risks not limited to risk in brain function and brain health related outcomes. And so her talk will highlight studies of the exposome, that measure of all the exposures of an individual of their lifetime, and how those exposures relate to health, and how that can contribute to tremendous disparities in health, but also holds the potential for action and for intervention.

She'll highlight uh the Neighborhood Study, which is a massive study incorporating 22 Alzheimer's disease research centers which examines the impact of the exposome on pathologic features of Alzheimer's disease, vascular brain changes and cognitive decline and she'll inform the audience about the Neighborhood Atlas which is amazing. It's a freely available data tool that provides regional Area Deprivation Index data for all locations across the U.S., effectively democratizing knowledge about disparities aligned, the disparities-aligned exposome for everyone.

And then, I cannot help, because it is so related, highlighting the student speaker who will round out the talks today. Jay Lusk, from Duke School of Medicine. He has actually used the Area Deprivation Index data to investigate whether or not socioeconomic deprivation strongly predicts mortality across a diverse spectrum of common neurologic disorders. Right — news flash: It does. To a great degree, and in fact, he may discuss that the degree to which it actually impacts mortality in some cases equals, and may exceed, some of the benefits that patients receive from some of our most heroic treatments. And so highlighting the importance of addressing these kinds of disparities.

And so, just to, to finish up, I'll steal a quote from one of my favorite science fiction authors who said that the future is already here, it's just not very evenly distributed. I'll say that as you've heard from our other speakers, the future of neurology, the future of advances in brain disease. They are here, or they are just over the horizon, right? But they are not distributed equitably. And so, if the promise of neurology is to be fully realized, then these promising interventions, therapies, have to be equitably distributed, so that all can benefit.

Frances Jensen reporting for Annapurna Poduri, "Somatic Mutations in Neurological Disease."

Ann Poduri's scientific panel was on somatic mutations in neurological diseases. It's largely focused on epilepsy, but it actually has a repercussions for other diseases. So it turns out that we know we have, everybody has their unique genetic makeup, and you've got the same copy of the genes, the same genes, in all your cells. We've also learned that, superimposed on that, many of you, of you have heard of the field of epigenetics, which means that genes that sit in your genetic programs in your cells can be turned on or off, or up- or down-regulated, based on things like stress or environment or age. So that's one way our genes can be changed in our brains from cell to cell.

Another way, that was discovered probably a couple of decades ago by Chris Walsh, who was at Harvard and Children's Hospital, was that you can have something called somatic mutations, which means that you can have all the cells in your brain have the same genetic program, except for a little island of cells that have something else. And they have like a little group of cells that can be sitting in a brain as a lesion, almost with a different set of genes being expressed. And they may be different in size, they may have different ah functional properties.

So if you can think about that, it turns out that epilepsy, a good portion of epilepsy is called focal epilepsy, where there's a small little island of cells that are generating the seizures in the brain. They look like a scar on an MRI, or when you do pathology. There are these cells that look abnormally shaped, and they have abnormal proteins, and they're firing at much higher rates, and are thought to be really generating epilepsy in these cases of something called focal cortical dysplasia.

Over the last few years it's been clear that actually these cells, aren't just acting strange. The reason why they're acting strange is that they actually have a different genetic program that started earlier in development. As our brains develop, a group of cells will divide and create like a linear column of cells above it…they're creating the cortical thickness, and they'll all derive from a couple of parent cells. And if your parent cell has a mutation, then that whole little population, that whole family of cells, if you will, have that mutation, and that's what we're finding focal cortical dysplasia is. So, really interesting.

And it turns out that the study of somatic variation, somatic mutation, has been studied in cancer. So the first speaker was Dr. Mary Armanios, who's an oncologist, and she works on the biology of these specific cellular changes in specific sets of cells, on how they give rise to cancer, actually, so that these cells kind of divide more frequently than the normal brain cell would, for instance. So she gave a first talk about how the somatic mutations create varying risks for developing cancer, and that was a great start, because it's coming from a field that has studied this phenomenon more.

Dr. Ann Poduri, who actually studied under, um, Chris Walsh, who was the person that first described this, has extended this field. She's incredibly well-known, and so extended this field into the clinical realm.

It turns out focal cortical dysplasias are a significant cause of childhood epilepsy. And so she was looking at drug-resistant pediatric epilepsies, and these malformations that you can see on a scan, which could be very big, or just very little, in a tiny little island of abnormal cells, or potentially half the brain can be different from the other half, and these can be very difficult to treat. And so she's been studying them over the last fifteen years or so, and has discovered that many of them actually are mutations that affect something called the mTOR pathway, the mTOR pathway, which is a protein synthesis pathway. So they're creating proteins at a different rate, a different kind of protein, these cells, and it can also make them more excitable. So she was saying, how far this field has come. This has really been revolutionary, and actually there are drugs that can actually target this pathway that we have in our armamentarium for other reasons that could be used, moved into that field. But more just the basic mechanism of understanding how these little changes in genes can cause massive changes in the structure and function of the brain.

The next speaker was Ghayda “Rayda” Mirzaa, who is a pediatric neurologist and geneticist, and he's modeling some of these variants in the lab. So we can sort of understand, and maybe actually understand, the genetic lesion that it's creating. And he uses, pursuant to the first

speaker, organoids from these, actually donated from the patients, so they can give blood, and then you can derive cells from some of their blood cells and make brain cells out of those and look at this, this fact that some cells have a very different genetic code than others.

So again, application of the organoids and to your point, why do we use them? And one day we can actually use drugs on those organoids and kind of do a drug discovery on that as well.

The final two speakers were Dr. Mike Lodato, who is a geneticist, who works on single-cell genomics, and he spoke about, maybe this isn't just in epilepsy. Maybe this is in other diseases, as well, because of course, we've seen it in cancer. So he looked at the fact that during aging you can have these glitches in programming of certain cell types, and he's starting to look at, in Alzheimer's disease, they surprisingly observed an increase in the number of these somatic mutations in brain cells derived from Alzheimer's patients compared to controls, so suggesting that maybe there's mutations happening in our cells in some of these neurodegenerative diseases. It's a very novel concept and very exciting.

The final talk was again back to epilepsy. How can we learn more about these focal regions in the brain? Dr. Jonathan Kleen, from UCSF, is sort of a bioengineer and one of the great things that's happened to neurology is that the engineers found us, and we found them, and he's created these incredible electrode arrays that are flexible, that a neurosurgeon can implant around a misbehaving part of your brain; like in this, in this case it was the hippocampus, where there's epilepsy, and wrap these soft electrodes around and record what's going on in these, in these cell populations, as if you could almost be recording from each of them exactly at the same time. And that is, you know he's hoping to take it into the human. He was modeling it in animals. And now has this work in miniature microelectrodes in humans. So again, showing how far the field of epilepsy is coming where it's really moving into genomics, into engineering and therapeutics and cellular mechanisms.

We do not have a representation from the final session which has just concluded, so they may be still in it. So I we will open up to questions about our other programs that you've heard about.

Question for Jack Parent on brain organoids:

Question from Healio: Are human organoids made from stem cells? And are they a human or a non-human primate?

Parent: All of the talks in the session dealt with human stem cell derived brain organoids.

Question from Healio: Great. And is there any fear in the community that stem cell research may be going backwards in direction after the Roe decision?

Parent: I mean, there's always concerns with restrictions on human fetal research and human embryonic research because we learn a lot from these areas. We also use cells that are

reprogrammed, so mature cells that are reprogrammed to pluripotent stem cells, and that kind of avoids that controversy. But, it's important to look at all the different types, because we don't want to miss anything great. Thank you.

Question: Why is it so important to be able to model brain structures in three dimensions?

Parent: So that's a very good question. So there, you can let uh brain organoids mature when you grow them in three dimensions for many, many months, even years. And you can't do that with 2D culture. So you get more mature cell types, but also we're interested for a lot of diseases in network function, and these are 3D brain networks, and that get recapitulated in 3D culture that you don't see in 2D culture.

Question for Dr. Sathian/Dr. Jensen

Question: Does the increase in these genetic mutations later in life in Alzheimer's patients, as mentioned in the somatic mutations plenary, potentially correspond with these accumulated brain injuries or disorders that appear to worsen neurodegenerative diseases later in life?

Jensen: Oh, that is so interesting! That was not covered by his talk specifically. However, acquired injuries to the brain could be, one could imagine, that they may induce cell injury and subsequent potential mutation of certain cell types. I actually asked that question myself, of Dr. Poduri, who you may be able to access by email to ask that question specifically, but it certainly is an excellent question. And you know, there are so many unknowns that we are studying now in neuroscience. But given that there is an association of brain injury to later dementia — we all know about chronic traumatic encephalopathy, and actually, there's also other degenerative diseases like ALS that are also associated with a higher history of prior injury to the spine or the brain, so we know that injury is a cumulative risk. In a way it kind of is the same theme as the exposome where we're saying, it's lifetime accumulation. Our brain cells are with us for life. And so there you're carrying this history, whether it turns into an injury, a scar, a change in your genes, epigenetic change, or somatic mutation, or accumulation of a toxic substance that is impairing all of these things. We're realizing we all carry this lifetime history with us, and actually the discussion in, in the exposome group, which kind of touched upon this too, said: We need to do a better job of asking people about this. We're becoming more aware of this lifetime accumulative history as being important in terms of exposure and stress, injury, pollutants, etc., and that this has to become more mainstream of what we ask patients.

Question for Dr. Jensen

Question from USA Today: I was just curious in terms of the exposome. We, as journalists, tend to be very skeptical about those kinds of things because they're so hard to prove. Is there a preponderance of evidence now? Are you comfortable that we are, that these are in fact cause positive as opposed to just coincidental potentially.

Frances Jensen: The work done by Dr. Greenamyre is extremely convincing, and shows that paraquat, for instance, rotenone, TCE, actually activate some of the pathways we know are responsible for certain groups of patients with Parkinson's. This LRRK2 pathway, for instance.

So what the point you're getting to is, what do we need to really drive this home? We need two things: we need a mechanism, mechanism, mechanism, emphasis on this research. Because, of course, right now, as you point out, it's correlational. There are associations, but we're now looking for mechanisms. So there's the speaker, Tim Greenamyre, who is an example of somebody who's actually done that and nailed it.

The other need is biomarkers. So the question is, wouldn't it be nice to know your lifetime exposure to trichloroethylene, which seems to be a really bad actor? By the way, that's in our environment. It's not banned. You may even have it in your garage as a solvent. It's used all over the place — like wouldn't it be nice if we had something that told us what our lifetime exposure has been so that we could see a patient and go, “Oh, my gosh! You are like at eighty percent of your max.” We do this with radiation, by the way, we have radiation badges. So it's something like that for these pollutants. That's probably a fair amount of research-years into the future. But that was identified by Dr. Woychik and Dr. Koroshetz as something they feel is really going to be important for us to study, to actually know what your lifetime accumulation is of these things. These agents are not going away sadly. The last fifty years has deposited pollutants in our environment that are here for a millennia, probably. And so humans are going to be living with these for a long time.

About the American Neurological Association (ANA)
From advances in stroke and dementia to movement disorders and epilepsy, the American Neurological Association has been the vanguard of research since 1875 as the premier professional society of academic neurologists and neuroscientists devoted to understanding and treating diseases of the nervous system. Its monthly *Annals of Neurology* is among the world’s most prestigious medical journals, and the ANA’s *Annals of Clinical and Translational Neurology* is an online-only, open access journal providing rapid dissemination of high-quality, peer-reviewed research related to all areas of neurology. The acclaimed ANA Annual Meeting draws faculty and trainees from the top academic departments across the U.S. and abroad for groundbreaking research, networking, and career development. For more information, visit www.myana.org or @TheNewANA1.

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