Project Sleep Podcast
"Narcolepsy, Immunology & Neurology with Dr. Emmanuel Mignot"
(Sleep Insights Series Episode 9)

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Dr. Emmanuel Mignot MD, PhD is the Craig Reynolds Professor of Sleep Medicine in the Department of Psychiatry and Behavioral Sciences at Stanford University. He is also the Director of the Stanford Center for Narcolepsy. Dr. Mignot is recognized as having discovered the cause of narcolepsy**.** Dr. Mignot received his M.D. and Ph.D. from Paris V and VI University respectively. He practiced medicine and Psychiatry in France for several years before serving as a visiting scholar at the Stanford Sleep Disorders Clinic and Research Center. Dr. Mignot has received numerous awards for his work and is a member of both the National Academies of Sciences and Medicine.

The Sleep Insight Series invites listeners to learn about this amazing adventure we take every night called sleep. Through these insightful discussions, we examine sleep, and our societies beliefs about sleep, from a variety of angles. We hope you'll learn some cool new facts and analogies that you can use to help us raise awareness about this under-appreciated one third of our lives. This is a written transcription of the podcast "Narcolepsy, Immunology & Neurology with Dr. Emmanuel Mignot" (Sleep Insights Series Episode 9) from Project Sleep. Transcription provided by Mirela Starlight.

Project Sleep is a 501(c)3 Nonprofit Organization, dedicated to raising awareness and advocating for sleep health, sleep equity and sleep disorders.

All guests and speakers express their own opinions. While medical diagnoses and treatment options are discussed for educational purposes, this information should not be taken as medical advice. Each person's experience is so unique, which is why it's so important to always consult your own medical team when making decisions about your own health.

Julie in intro: What are the connections between upper airway infections, our immune system, and our brain? In today's podcast, I'm honored to speak with the 2023 breakthrough prize winner, Dr. Emmanuel Mignot, director of Stanford Center for Sleep Sciences and Medicine. We discuss new advances in our understanding of narcolepsy as likely an autoimmune disorder brought on by genetic and environmental factors. And please note that we recorded this in April 2020, when the COVID-19 pandemic was still very new, yet this discussion remains timely and important, as we continue to learn so much from the frontiers of immunology and neuroscience.

Julie: Hello, everyone! We are just so excited to have Dr. Mignot. So I don't know if you guys know, Dr. Mignot and I were both in Australia years ago, for a wonderful conference hosted by Narcolepsy Australia. And this is where I learned that Dr. Mignot is quite the dancer.

Dr. Mignot: I don't know, I do my best, but it's true I enjoy it, but— I mean in France I think we dance a little bit more, so that comes a little bit from my— education, you know, I mean.

Julie: (laughs) And I don't know if everyone knows that Dr. Mignot's dog, Watson, does have narcolepsy with cataplexy. So, how's his cataplexy?

Dr. Mignot: I'd say it's still the same, I mean I think it's hardest when we walk actually, for a long time. Then at the end or some time he's just exhausted, sleepy and he just can't move anymore. But the good news about a chihuahua is that it's really easy to carry, and he's very easy going so (laughs) it's not a big problem.

Julie: Well, with that, let's go ahead and get started and talk about, since September of 2018 there's been a lot of advancements in our understanding, thanks to you, and to some other research groups— in understanding type 1 narcolepsy with cataplexy and more about the genetics and some of the environmental factors so, can you give us an update?

Dr. Mignot: Yes, I think now it's more and more clear that the course of narcolepsy type 1 is really this autoimmune process, where the immune system gets triggered by the flu, and starts to attack certain pieces of the flu that resemble hypocretin orexin, which is a chemical in the brain that helps to stay awake, and when the immune system starts to confuse, you know the flu and these cells that produce hypocretin, that destroys them, and once you don't have hypocretin, this is the cause of type 1 narcolepsy. And uh, that's relatively simple.

Julie: Well you make it sound simple, my goodness. For the environmental factors, do you think it's just flu or could it be other things?

Dr. Mignot: So, we don't know. Probably flu is a big one, but strep also has been suggested. Strep throat. And I still believe it's involved, as well, that you know if you have the flu and strep on top of it it makes it worse. Whether or not we'll discover some other things that could cause it or trigger the immune response, it's always possible because nature is very diverse, so there must be a lot of different bugs or virus that may have sequence that could look a little bit like hypocretin. So of course you're going to ask me if coronavirus is going to trigger narcolepsy, is that right?

Julie: Well, at some point, yes I was going—

(Dr. Mignot laughing)

Julie: — to ask something like that. (laughs)

Dr. Mignot: Yes. Actually someone from the CDC asked me that question, and— it's difficult to be sure, but probably not. Because I think we would have noticed it before, but it's not possible to really be sure that it could not have a sequence inside that could resemble the hypocretin. 'Cause one of the thing we've discovered actually very recently is that it's quite difficult to figure out, based on the sequence, you know just looking at the sequence of the flu peptides and the hypocretin, what really resembles hypocretin. We don't have a good model. It's more in three-dimensional space that it needs to resemble, and it's not very easy to make a model to see what really resemble hypocretin. So it's always possible that there will be something in the coronavirus that resemble hypocretin, but probably not.

Julie: Can you explain that little piece a little bit over again for me? So, the flu has a piece of it that mimics— or no, not mimic— it looks like a hypocretin cell?

Dr. Mignot: Yes. So, exactly. What happen is there's a little piece of the flu that looks a little bit like hypocretin in it's sequence, in it's structure. So that when the immune system— the immune cells that are recognizing the virus, they take the virus, they kind of chew it up in small little pieces, and then they recognize specific pieces. And one of these piece looks like hypocretin. So it starts to attack the virus, recognizing this piece, with special receptor. And then at one point, we don't exactly know why, there is some hypocretin floating around close by, and it starts to recognize the hypocretin and then it gets more and more directed towards hypocretin and then it starts to think that the hypocretin is just a flu, and as a consequence it attacks the cells that produce hypocretin, like if they were flu infected cells. And then at the end they are all dead and you have narcolepsy.

Julie: And why is it certain people that that happens to?

Dr. Mignot: Ah. So there are probably many different explanation. One of them is genetic, because the way our genetic system reacts to flu infections or to infection in general, is very personalized. And it's very useful because otherwise if a new flu was coming about, or like the coronavirus for example, we don't know why some people are very sick and others are totally fine. In fact, we know of course that if you're old and you have a lot of comorbidity you have a lot more chance of having a very severe coronavirus, but there are even kids that sometimes die from the coronavirus, or young adults. And almost surely they're genetic. Because everyone has a slightly different genetic makeup that makes them able to direct immune reaction against different pieces of the coronavirus. And that makes us better able to fight the coronavirus if it mutates in different areas, because this way we're not all attacking the same piece of the coronavirus. And that's a little bit the same for the flu and narcolepsy. There are some people that attack more a certain piece of the flu, and others that attack other pieces of flu, and that depends of certain of their gene, in particular one that's called HLA— which some of you that are nerds like me, you know— (laughs) know about it. There is a gene correlation that is predispose to narcolepsy. And this HLA gene has like, many, many different variants, and there's only one particular variant that predispose to narcolepsy. That's called DQB10602. That 25% of the population has. And you need to have this particular variant because this particular variant sees a piece of the peptide of the flu that looks like hypocretin. If you don't have this particular piece of HLA subtype, which about 25% of the population has, you are going to bind other pieces of the virus, that don't look like hypocretin. So that's why, at least the genetic play a big role.

Dr. Mignot: And I'm sure for coronavirus we're going to discover same thing. That the people who are very sick probably have certain HLA subtype, for example. And maybe we'll also discover that maybe some people after coronavirus will have strange complication, you know, autoimmune disease, that's very possible. Depending of their genetic makeup. So, definitely some is genes. There are also genes that are very important with how we react to the flu. We have even found certain genes that patients with narcolepsy have more than controls, that process a little bit differently the flu— or make the immune cell more reactive to the flu. And all this makes you more susceptible to narcolepsy. And in addition to the genetic, we know that there's just bad luck that happen. Because many people get the flu and many people have the genetic makeup, and only a very small percent get narcolepsy. And the bad luck is at least

partially due to, probably the type of infection you have had in the past. Because your immune system learns every year, every time you get a new flu it just learns this new flu. And it kind of adapts itself over the years. So the state of your immune system depends of what you have experienced as infection since you have been born. And that's why— even twins! That have exactly the same genetic, if you really look at their immune system, after 15 years it's quite different. So there's definitely your past— you know, past serious infections that also makes you more or less receptible to narcolepsy. That's why actually we even have hope that one day we might even be able to maybe vaccinate people to prevent them from developing narcolepsy. Because we might be able to make their immune system go in a certain direction, against the flu, that will avoid them to develop these immune reactions that is confusing the flu with hypocretin.

Julie: When is that coming?

Dr. Mignot: Ah! (laughs) Ah, that's a good question. I think we could try now. The problem is, you know, narcolepsy is not that common. And people are always a bit afraid of tinkering with nature a little bit, you know. Is that worth it to do it, considering that there are so few people who will develop narcolepsy? It's very difficult. You could— you never know. By pushing the reaction towards narcolepsy, maybe you could create another problem. You can never be absolutely sure. I don't think so. And I think eventually when we'll know more, it will be done. But— let's say that right now I think we need to do a little more research before doing that.

Julie: Yeah.

Dr. Mignot: I think where it could be very helpful, is for example, Julie, in your brothers or sisters— or, you know people who are family members. Because there's more chance of developing narcolepsy, we know that. It's not a huge risk, it's only about 1% if it's a brother or sister or a child. So it's not like something to be worried about. But 1% is not negligible. So for these people I think it could be worth it to develop a special vaccine or something that you could give them when they're young and will avoid maybe them to ever develop narcolepsy.

Julie: People that have that DB— I'll get it wrong, but that genetic marker? That's still a quarter of all people, right. That have that.

Dr. Mignot: Yes. So I think, yeah. Even in patients who have— so the chance of developing narcolepsy in the general population is about one for 2-3,000 people. If you are DQB10602 positive, it's about one for 800 people. Okay? Still low, okay. But if you add all the genes, we're actually now doing that— if you add all the genetic predisposition, you could tell actually exactly what chance everyone has to develop narcolepsy. But still at the end, I think we still would come up with— all, you know, even if you— I take your genetic makeup, I would probably say oh, Julie has one for 200 chance of developing narcolepsy. I would never be able to say from the genetic, Julie, that's it, you are going to develop narcolepsy. But when you go to one for 200 or one for 100— like family members of people who have a high genetic loading, it might be worth it to consider a vaccine, slightly different, and would prevent the development of narcolepsy but I think it will take a long time before this is done. Unfortunately. I wish that things would move faster, but. I think you have heard also, all the discussion about how complicated it is to introduce a new vaccine, and of course— all of you know that there were one particular vaccine that even triggered narcolepsy. So— it's always a risk/benefit ratio, to try something new.

Julie: So, you— there still needs to be stuff to figure out about the genetics and about the immunology, right.

Dr. Mignot: Exactly.

Julie: Okay, and then—

Dr. Mignot: Because you're right, if we somehow are able to really understand this process completely, you know, we might even be able to see which one are highly at risk because for example there may be some people who already have the cells, that are ready to be activated by the virus and could be then killing hypocretin neurons. Maybe these people is only one percent out of 10, of narcoleptics. And then those it might be really worth it to prevent it. So if we could discover the exact cells in the blood that are dangerous, we might be able to find a way to avoid them to be ever activated. So— you know, this is the fun and also the frustration of research. You know, we— it's a little bit like you are trying to narrow down and narrow down, narrow down until you really get to the final answer and I think we still have to learn about the immunology to be able to really predict who is going to develop narcolepsy. But it might be possible that one day we will be able to take a blood sample and say, oh, this person is really at very high risk because they already have the cells that are dangerous, and those maybe, we could use a vaccine to prevent it.

Julie: I just think it's so fascinating, Dr. Mignot and I had a phone call a few weeks ago that sparked my idea to do this, because Dr. Mignot actually recommended a book to me about five years ago, I think when we were in Australia.

Dr. Mignot: Ah-ha!

Julie: Called "The Great Influenza". And so I had read that five years ago, not realizing, you know, of course, how it would be so—

Dr. Mignot: Relevant.

Julie: (laughs) Yeah. But I remembered this specific chapter and I went back and looked at it again, how after the 1918 flu, it took a while, too— it wasn't always immediate, but there was um, Parkinson's like symptoms— and there was even an interesting form of schizophrenia, that some people developed. And so this kind of this idea, I think our society hasn't quite caught up to understanding how flus and influenzas and— that immune systems' interaction with the brain and neuroscience.

Dr. Mignot: I think you're absolutely right. I want to say one thing about that is— what is the most complicated organ in the body, is the brain, right? I mean we know it's super complicated. Actually the immune system is as complicated. Because every minute, you know we have, I mean— if you ever take a petri dish and of course you spit on it— I don't advise you to do it, but a lot of things will grow, pretty disgusting. You know, streptococcus and more, you know, it's beautiful. But even if you take like the surface of your skin, we have five more— you have heard that your microbiome— we have far more bacteria than we have human cells. So it's an

enormous amount of bacterias and viruses that are always in constant synergy with you. And of course, its— I'm sorry to say, but— I still believe in natural selection. (laughs) It's kind of natural selection in action. Every second. So the day you are dead, I mean I'm sorry but you just start to rot from the inside because the bacterias just— are not enough kept, you know, by the immune system. So we are constantly fighting, even our own bacteria that are friends of ours. We still tell them, you know, just don't go too much, you know. So the immune system is more kind of a general equilibrium, and sometime we get this completely new— new flu, or new bacterias. But it's incredibly complex, it's really our whole interaction with the outside. And I think it's estimated that there is about 10% of all the genes in the body that have a role in the immune system. It's absolutely huge.

Dr. Mignot: So, we are discovering that more and more disease are going to be related to infections and in ways that we did not understand. And for a long time, people have believed that the brain was immuno privileged. You know this is the story of mankind as well, I mean if you read a lot of history book, we didn't— we thought that we were in the center of the universe, of course. The Earth is in the center, and then we discovered we run around the sun, and then after, you know we probably thought that we were— Europe was the only center of the universe, and of course that's not true. And then after we believed that we were, you know, different from all animals. And we realized that we're the same as all animals. And then we discovered that we have a very different conscious and we're different from animals but now we are realizing that animals have very complex behaviors and they— there was one paper recently, it just came out, that suggested that certain monkeys already have all the instruments for language.

Dr. Mignot: So it's clear that the more you realize, the more we see that we are not different from animals. And in the same way, of course the brain is considered the cool organ, you know, my god the brain, that's— that's us, you know. But actually I think we're really underestimating a lot, what the peripheral body can do and I wouldn't be surprised for example, if when we measure proteins or— even gene expression, in different parts of the body like the liver, you can actually find many— like, about 10% to 30% of the gene of protein in the liver, they change with sleep. So it's like if the liver was sleeping, himself. So I think we definitely overestimate probably a little bit, our brain. And the second thing is we have always kind of looked at it like it's immune privilege, that the immune system didn't go there— that it wasn't at all affected because it's so important, because we're so unique— and now we realize that it's not very different from other organ. That cells of the immune system go into the brain, and they make sure that the brain is not infected, like the rest of the organs. So—

Julie: Right.

Dr. Mignot: —the same way they can be subjected to autoimmune disease, like narcolepsy. But this is a relatively new concept, I mean, this was really not believed to be true, even 10 years ago. Now there is a lot more interest in understanding how the immune system works in the brain and many people believe in many, many more diseases than just narcolepsy.

Julie: Right.

Dr. Mignot: Schizophrenia, and Parkinson— exactly.

Julie: Can you tell us a little bit more about what happened in 2009 and 2010. So you alluded to a vaccine causing narcolepsy. But can you go over just briefly like what happened with the H1N1 flu?

Dr. Mignot: Yes. So, I think that's good because maybe I can teach a few of our listener about the differences between the coronavirus and the flu. Genetic material comes in two flavors, DNA and RNA, generally, and DNA is what we have in our cells. And RNA, a lot of virus have RNA and instead of their DNA. You know RNA is something we produce in our body, to produce protein, but it's not our genetic material that we use to translate— to make babies, you know. We use really DNA as our core genetic material. And the virus, like both the coronavirus and the flu, are RNA virus. Which are actually more common than DNA virus. And one of the issue with RNA virus is that they have to be transformed into DNA to be reproduced inside the cell, because a virus is like a parasite. What it does is really uncheck it's genetic material and try to use as much as possible of our own cellular machinery to reproduce. So, it can't reproduce by itself. So, in fact a virus is at the border between being alive or not. You know a lot of people ask what it is, is a virus a living organism, or not? In theory it's not a living organism, because it cannot reproduce by itself. Bacteria is life, because it can reproduce by itself. You give it nutrient and it reproduce by itself. But the virus, it can't. It has to have a host and it's going to use the host machinery to reproduce itself. And when it's an RNA virus, it needs first to be transformed into DNA. And as a consequence, one problem is it mutates a lot, because it makes a lot of errors when it does that. So the RNA virus are a little bit more dangerous, because they mutate more. They change over time, more. Which is good and bad because at the same time the coronavirus, like the flu, is going to evolve probably to be more— happy with humans, you know. And it's not the advantage of a virus to kill everyone. Because, it rather like, make them sick and go to next person. 'Cause if kill everybody, you know, it's not good for natural selection, the natural selection is not going to function, it will immediately die and the virus will disappear. That's why Ebola, which is so bad, has never been like a huge epidemic because it's too lethal. But right now we have a new virus that at the same time can reproduce a lot and is also quite dangerous.

Julie: Can you describe about the H1N1 and what happened? And how narcolep—

Dr. Mignot: So the difference— so the slight difference between the flu and the coronavirus also, is— I mean it's technical but, that the flu is in some ways more dangerous because it has what we call a segmented genome, that means that the chromosome of the flu, there are several chromosome. Instead of being just one piece of DNA, it's several pieces of DNA. And as a consequence, some time it kind of get mixed up with another flu from another species, usually swine or bird. And then it reassort it's chromosome, and suddenly you have a very, very mixed virus that's half bird or half swine and half human. And then this one goes through the population, and that's a new virus. That can be very dangerous. We call this animal flu, that suddenly go into human, it happens once every 50 years. And when it happen it can be really horrible, so you mentioned the 1918 flu. It killed about 100 million people, that was really awful. And I think we can learn a lot from this to apply to coronavirus. Then there were another flu like that in 1957, it probably killed about 200,000 people, so that was a lot of people as well. Then there was a flu called the Hong Kong Flu, in 1968, and interestingly— so until 2009 the flu that were circulating were the descendent of these flu, that came from animals, that had adjusted to human. So every year you get almost the same flu that just has these new mutation, and you just need a vaccination that change a tiny bit, and you are relatively protected already because you have already seen the flu.

Dr. Mignot: But then when these new flu happen, and in 2009 there was another one that came out of swine— it can be very dangerous because you may not have any immunity and the virus is much more nasty, as I explained, because it has not adjusted to the host, with all these new mutation. And that's what happened in 2009. And we had already suspected that narcolepsy had something to do with the flu or strep throat, because we had noticed that in young kids that develop narcolepsy, very often they had upper airway infections or strep throat and then they develop narcolepsy during the summer. So, in kids narcolepsy is very often very abrupt. In older adults, some time it starts over a period of a year, so it's a little hard to say when it started. But in kids it can be very, very abrupt. Suddenly someone develop narcolepsy, sometimes within a week. You know, the child was completely fine, he's 7 years old and suddenly he falls asleep all the time, and gain a lot of weight. And the parents sometime can tell you, oh this started the week of March 15th— you know, there's no doubt he was totally fine before. When narcolepsy started in these young children it was always starting during the spring and the summer. So that with the strep and so forth, we already suspected that some infection during the summer were triggering narcolepsy.

Dr. Mignot: But then when you had this new flu that happened in 2009, the Swine Flu, people panicked, exactly like coronavirus, except that— thank god it was not as bad as coronavirus. But it started in May, in Mexico, and initially people thought it was going to be as bad as the coronavirus, because people— what we call the case fatality rates, the number of people that come sick in the hospital and that need really— and die, was about .6%. So coronavirus it's about 1.2%. So it's higher. But it was still very high. But that was overestimated, clearly, because there were probably a lot of people that had it that never had symptoms. But still, people really thought, my god, this new flu is going to be like 1918. And that's why they pushed this particular vaccine very, very quickly. And like coronavirus, it's a little bit better, because the flu, we already create the flu vaccine every year, with these old strain that circulate. So creating a flu virus with a new strain, it's not that hard, it's a little bit like plugging in the same process with a different flu. So they really hurried the vaccine very fast, you know from May, they could get it in December. Because they were very afraid of the following winter.

Dr. Mignot: But then there's one particular company that made a particular flu that we don't really understand— flu vaccine— in Europe, called Pandemrix, and you have heard of it. I believe probably it's a bit too strong, and very special, and I think we actually found maybe— we have an idea of why it was particularly bad, I think one of the ways the protein of the virus were extracted, maybe created more of a problem. And it kind of seems to have triggered a lot of cases in Europe. But the virus itself also increased the number of cases. So clearly it was just a virus that sometimes was confused with hypocretin. But with a vaccine that maybe was a bit stronger, and the composition a bit different, this effect was even magnified. So a lot of people developed narcolepsy after this particular vaccine. Only in Europe. So of course now we are a little bit in the same situation. So now, since 2009— every year you are getting vaccinated, I hope— because I'm totally pro vaccine. Because the flu still kills, you know, 25-50,000 people every year. Especially old people. And, you are being vaccinated with this descendent of this H1N1 swine flu. There's just a tiny bit of changes that are accumulated in the last 10 years. So, they grow in eggs a descendent to be as close as possible of what circulates now, but it's very similar to what it is. And it's also a descendent, second strain that is put in, which is from 19— I told you in 1957, that's still circulating, that's called H3N2. And they get also another influenza B but that's not very important. So it's like, every year that's what we get as a kind of a booster.

Julie: Well, I— so we won't know when another flu— I mean, I understand better from what you've just said that the swine flu from 2009 was this new, you know, thing, and—

Dr. Mignot: Yes.

Julie: —we won't know like if— whether corona or any of the bird flu, if any of those are gonna cause an upsurge in narcolepsy, until we're able to do that 3D modeling—

Dr. Mignot: Yes.

Julie: —you mentioned earlier?

Dr. Mignot: You're right, you're right. But in general, you know, it has more chance to be a flu, because— a flu looks like a flu. (laughs) And we know that the flu is— resembling, certain pieces of the flu are resembling, you know, hypocretin. So probability that a piece of coronavirus would resemble hypocretin is much lower. But—

Julie: What about the, um— strep throat. Does strep throat look like the hypocretin?

Dr. Mignot: Ah. The difference between the flu and strep, is about the difference between a lizard, and a human. A bacteria is a million times more complex than a virus.

Julie: Oh.

Dr. Mignot: So, to give you an example— the virus, like the flu has only, I think 13 proteins. 13 different proteins, because it uses— it just has the minimum needed to reproduce itself and to use the machinery of the cells.

Julie: Well I guess while we're on this topic, I remember you mentioned you have been working, possibly, I think was it, on vaccine and vaccine side effects. Have you been helping with any of that as far as COVID-19?

Dr. Mignot: Yeah, so what we do in narcolepsy is actually very applicable to coronavirus. I still focus on the flu itself, because I'm a narcolepsy specialist and I want to solve your problems— (laughs) but everything that I'm learning about the different pieces of the virus and how they interact with the immune system, to produce these reactions, I think is absolutely— and represent— applicable to the coronavirus. Because on the forefront of understanding this and you know, it's pretty much the same problem. I mean in fact it wouldn't be very difficult for me technically to do similar studies with the coronavirus. Trying to understand how the coronavirus is recognized by different people. It's just that, uh— I mean, I'm more focusing on narcolepsy, but. Knowledge is always transferrable.

Julie: I did want to ask you a little bit about narcolepsy type 2 and idiopathic hypersomnia. It's really been evolved, I think over the last five years as far as our understanding of what those conditions are, and— you know, what can you tell us about how we're kind of like coming to some better understandings?

Dr. Mignot: So I think we are— at the destructive phase, okay. What I mean is that we have had a lot of assumptions. Made a lot of assumptions about what these problems are. Whereas we knew absolutely nothing. Like, idiopathic hypersomnia is different from narcolepsy without cataplexy, it's very clear from more and more studies that there's no real limit, you know it's like— it's almost like the flip of a coin. You do an MSLT, which is a test that we use— sometimes there's SOREM, sometimes there's no SOREM. If you don't have narcolepsy type 1, it can be just random. And it's pretty awful because some people are treated because they are called narcolepsy type 2, and others it's much harder with the insurance, whereas they have exactly the same problems, they suffer as much. So, everyone realized that there is a problem. And that we need to come back and figure out a way to better study this condition, and better realize where the subgroups are. That doing this MSLT to separate the subgroup is probably not the right way to do it.

Dr. Mignot: But the problem is, like for in a lot of cases when you come back it's also a little hard. You just have to step back to better jump, as we say, and that's exactly where we are. But I think we have a lot more hope. And one of the big hope I have, is thanks to new technology. I mean I haven't discussed that much in this talk, but— I have a little piece of myself that does a lot of machine learning and high computer science as applied to narcolepsy, and for example now we can diagnose narcolepsy based on a night sleep study. Just by the brainwaves, during the night. We don't really need the MSLT. Even so it's not yet in play in practice, we feel very strongly it works as well. So in theory, you could just do only a sleep study like for sleep apnea and know if you have narcolepsy. So that's already a big progress. But we also know that just doing a sleep study is not the best way. The best way would be to give you something that you can wear, for three days, continuously, move around, do whatever you want, go to bed. Like a little cap. And then we will see exactly how is your sleep and your wake, in a natural environment. And then we will really know your problem. I am a big believer in how people live is really the key, is that right? And I think we need to apply this kind of new technology to narcolepsy and hypersomnia. And for narcolepsy type 1 it won't change that much, because we have very good diagnostic procedure, even the MSLT works well. But I think for hypersomnia, we will probably realize that there's very different types of waves in different people— and I'm sure that they will have different treatment— and I think we will make a lot of progress.

Dr. Mignot: So my opinion for hypersomnia and narcolepsy without cataplexy is we're a little bit in a destructive phase, but at the same time with the new technology that's coming, we have the opportunity of looking at it in a new way, that I think is going to make a lot more difference in how we treat it. And also the other positive of course is that we have all these new treatments coming in. I mean now there is a lot of interest in helping people who is tired and sleepy, and of course there is drug to replace orexin, hypocretin. There is histamine drugs. I mean, there's a lot of interest in helping people with this kind of problem, staying awake. But I think right now it's like we take a dart, and then we throw it at the patient and we just hope it's going to work. And that's pretty much what I say to my patient. If they have narcolepsy type 1 it's pre-qualified. But for narcolepsy type 2 or idiopathic hypersomnia, it's trial and error. Of course there is a little bit of intuition. I mean, every doctor will tell you this. You know, I know very well what to do, but the truth is I just— it's a little bit of intuition, but— it's not worth much. It's really trial and error.

Julie: I think that's true for everyone, I mean because all of our bodies are different, so— but.

Dr. Mignot: That's true, but for narcolepsy type 1 for example, there is still like the same biology, exactly. The expression of a response is much more clear, you know. And we see it pretty consistently. And of course when you have orexin agonists, or hypocretin agonists, of course it's going to be even more clear, in my opinion.

Julie: Yeah. So, I just am so glad that there's more research and interest in this area, because I for a long time felt like most of the research or all of it was in narcolepsy type 1 which of course is what I have and so it's important but— I know a lot of people have type 2 narcolepsy and idiopathic hypersomnia, so.

Dr. Mignot: Yes.

Julie: There is— it's a very— like, I don't know if I'd called it destructive, but there is a phase of movement right now.

Dr. Mignot: Yeah, I don't know if destructive is the right term, but I think we are really looking at it again, in a more objective way. And it is really good. I mean I think it's going to— yeah. I suspect we will define new types of disease that will be much better the target of specific medication. We just need to do more study. And by the way of course I have always been interested also in idiopathic hypersomnia and narcolepsy type 2. But the reason I have not studied that, is first that— narcolepsy type 1 seems to be much better defined. So I knew it has more chance of finding a result. I didn't have to do this, where I'm trying to redefine the problem, you know. It was already very well defined. And also now it's mostly solved. So, I think definitely a lot more people, including myself, are going to work on these other conditions.

Julie: Good. I like that. You mentioned a few things about treatment, but let's go over that a little bit more. So there have been a few treatments that have been recently FDA approved. Tell us a little bit about those.

Dr. Mignot: Yes, so— there's one that's called pitolisant. Which is working, so most of the drug— first I should mention the drug that we have right now, that work on narcolepsy, they're pretty much of three classes. One of them is stimulants, it's a little bit like amphetamine, or modafinil. And they mostly work on a chemical called dopamine. Then there are antidepressants, and they mostly work on norepinephrine and serotonin and they work on cataplexy, so they are not used as much for idiopathic hypersomnia, even so— sometimes it can be beneficial. And then there is Xyrem, that helps people to sleep at night. And clearly these drugs sometimes can help idiopathic hypersomnia or narcolepsy without cataplexy, but as you see, they work on— dopamine, norepinephrine, serotonin, for antidepressant, and for GBH it's probably GABA. And these new drugs that are coming, one of them is called Sunosi, which is working both on norepinephrine and dopamine so it's a little bit different than modafinil. And it's still in the same class of drugs, how it works, than the stimulants. But it seems to be better— more effective, than modafinil, without having the big problem of amphetamines, that are kind of too strong. So definitely I think it's a drug that will help more patients than the traditional drug. Then there's a new drug that works completely differently, that works on histamine. You all have been taking antihistamine, and you all know, for allergy— and you all know that it makes you sleep. So this drug does the opposite in the brains, but it doesn't make your allergy worse, but it makes you more awake. So general feeling of the drug is that it's a drug that helps to stay awake and reduce also cataplexy if you have cataplexy. But it's certainly not like, a proactive

compound, you know it can help some patients and I suspect it will also help a lot of patients with idiopathic hypersomnia. We just need to use it more to really understand better which patient would benefit. But the big advantage of it is it clearly is different. It doesn't work the same way as amphetamines and all this other drug. So I think we have already two new, completely new drugs.

Dr. Mignot: And then finally of course, most exciting for me is that there is these new drugs that are coming that seem to be able to replace orexin hypocretin which basically are— could replace what's missing in narcolepsy type 1. And it seems to be very spectacular in patient with narcolepsy type 1. It really kind of makes them completely awake, I mean there's one study that was done. Nothing that has been tried worked so well. So there is a study where they have taken patient with narcolepsy type 1, and they use a test called the Maintenance of Wakefulness Test, which you know. It's a horrible— it's a torturer for narcolepsy. You ask them to stay awake for 40 minutes, four times a day. A patient with narcolepsy basically can't even stay for— three minutes. I mean in a dark room like this, you tell them, stay awake— I mean that's just against the nature of narcolepsy patients. They fall asleep in two minutes. After the drug they could stay awake for 40 minutes, the entire time of the test. Nothing that I've seen ever has been able to do that. So that's a big hope for patients with narcolepsy type 1.

Julie: It's just starting right now, right. The clinical trials in the U.S. are just starting.

Dr. Mignot: Yeah. And the good thing is that, there is another— it worked also, in people with idiopathic hypersomnia or sleep apnea, for example. You know people with sleep apnea sometime act tired and we can't really get them back to normal and we don't really know why but it's really not due to the lack of orexin, but it still made them more awake as well. So it works also in normal people. So I think it could very well help a lot, you know, patients with idiopathic hypersomnia or narcolepsy type 2. And it's not because it's not the cause of the problem, that it's not effective. We use drugs for pain— you know like, if you have pain you take opioids or anti-inflammatory and sometimes they work even if you don't have an abnormality in the opioid system. I mean, there are symptomatic treatments. So, I think that there is big hope that this will make a big difference. And you're right, so clinical trials are being started— unfortunately they were interrupted because of the COVID-19, we can't do anything, everything was stopped. But I think they will restart as soon as we are done. I mean, for us, since Stanford asked for a lot of people, it just gives us more time to do the paperwork, to start the trial.

Julie: If people want to look for clinical trials, clinicaltrials.gov is a good place to look, and search for narcolepsy, and get more information because it is a great way— unless we have people that are willing to participate in clinical trials, we can't get new treatments, and so we do—

Dr. Mignot: Yes, you're right. And I like to say what's a little tough about clinical trials of course is that first you may be on placebo. So often— always, you have one arm where it's placebo and one arm where it's active. And the thing that can be very frustrating is that, it may work great, but then, after, you can't have the drug. They will tell you, I'm sorry, we need to wait until it's approved. So sometime it can be almost like a taste of what it's going to be and then you can't continue. But still I think if we don't have anyone you know doing this kind of study then it will never be available to anyone. So—

Julie: Right.

Dr. Mignot: That's why I'm hoping that it will happen during the summer. Because, you know the summer is a good time for example for students that are already in college, or it's easier for people to take some time off, you know. Because since they have to stop their medication, it's easier for people to do it. Yeah.

Julie: Yeah. So, definitely— if you can, that's a good thing that you can help to advance science in. We always are looking— it's just exciting that we have clinical trials finally in the narcolepsy space, so. Is there anything else on treatments?

Dr. Mignot: No, but I really do think that what I was telling you about monitoring and being able to have this new technology, right now the problem is everyone is measuring sleep with their watch. I'm sure you all have this ding-ling-ling. And we know that it doesn't really work very well, because it measures activity. So if you don't move, it says you sleep. Because it just can't measure your brain activity. But now there's some new devices that can measure brain activity, and that you can wear at home and the data could be directly sent to the, you know, to a clinician. And I really hope that in the next few years we'll be able to have people really wear these things for several days— and we'll really see— that will be useful, not only for potentially diagnosing patients, you know understanding really what the nature of their sleep attacks, and so forth— so when they are spaced out, what's happening in their brain. But also, potentially, titrate the drug. To really see that it's really helping the patients, on their actual symptoms.

Dr. Mignot: So I'm very positive, I think the development of new technology is also going to really help a lot of patients to get better treated. Because often we are just working in the dark, you know, we just titrate. And some people, including myself, we are not always very good judges of how we feel. It's very difficult to judge really completely how you feel. That's why of course when I talk to patients, I often like if— certainly children, it's very helpful to talk to the parents. Because sometimes the perception of the patient is different. Very often patient with narcolepsy underestimate their symptoms. They're oh, I don't have cataplexy anymore— but in fact, you see them having cataplexy all the time. And so having an objective measurer is really helpful. And I'm really hoping that will help to treat better patients, as well. So, it's not only drugs, I think devices are going to help a lot.

Julie: That's exciting. I didn't— ahh, that's great! Thank you for sharing that. So, I wanted to ask you a question, it was my favorite question we got back in 2018 when we did our broadcast, which was, "What keeps you up at night and what energizes you to get up in the morning?"

Dr. Mignot: I mean, for narcolepsy patients? Or personally?

Julie: Just like, well I'll go first, how about that. Okay.

Dr. Mignot: Yeah, go ahead.

Julie: For the narcolepsy community I'd say what keeps me up at night is— I think, worrying about whether we're doing enough on the advocacy front and I know we're already doing a lot and we're doing more and more and I'm so proud of that, but I just continue to think— we've

focused a lot of our efforts at NIH as far as the NINDS, which is one of the institutes there. And now Dr. Mignot's research is actually more in immunology, which is actually a different— department, or institute, at NIH. We haven't focused our efforts on that as much, so. And then a thing that energizes me to get up in the morning, is I'm super excited to be working a lot more, and actually even talking to Dr. Mignot recently— about social support, and I just think that the social experience of narcolepsy has been underrecognized. A little bit like how Dr. Mignot, you said like, we thought the brain was the thing— you know, and then you realize there's the body. And then I would say, there's the body— and then there's also all the people around the person with narcolepsy. And I think that, you know, family and friends and the impact that a community and society has on our experience with narcolepsy is underrated. So there's my answer. So what's yours?

Dr. Mignot: So I would say that definitely what keeps me up at night is the funding. It's just like, you know, we always are struggling with, to write these grant. And they get rejected by people who don't know what they're talking about, I'm so sorry, but— you know for example I told you this HLA-DQB10602, the last time I submitted my grant to NIH, I mean there's hundreds and hundreds of studies that have shown that it's like, 97%— that it's really all the same disease. And one of the reviewer said, oh, but— you know the disease narcolepsy is complicated, it's not just one mechanism for narcolepsy type 1, and it's just— you have people review your grant, you take— 9 months— months— of writing it. You submit it and then you have people who don't know anything that spend 10 minutes and destroy it. And then you read it and you see they're completely incompetent, and you have no way of doing anything. That's really hard.

Dr. Mignot: Then, what energizes me the most I mean I have to say still, the new agonist. I'm so excited for patients, you know. If it works as well as it looks like— I mean, this is going to be a real change for a lot of people. And I think we are very close to really making a dramatic change in the diagnosis and the treatment of this disease. That will be so profound that people that have narcolepsy won't have the same life, that people who have had it today. And I mean, when you think about that it's just unbelievable. I mean it just— all this suffering that will be gone, I think is— for a generation. You know, it's not just now. It's going to be— forever. And that's what's really exciting about research, too, is that not only you can do a lot of good for a lot of people, but also there is this discovery process, which is really amazing, you know, it's discovering something new— there's nothing more exciting. So, I don't have any problem being excited.

Julie: I really like how the birds started chirping behind you as you started talking about what made you hopeful. So, I feel like the birds are on our side.

Dr. Mignot: It has never been a better time for patients with narcolepsy, the future is really bright.

Julie: Yeah. And I think that was really humbling for me to realize, when I first started treatment in 2007, you know I didn't like— I was like, these treatments are so challenging— and then, when I started studying the history and realizing that you know how many people had fought to even make those treatments available for people like me to be diagnosed in 2007 and to then to be like, ugh, these treatments are terrible! Like— other people fought so hard to make those available. And they have been. You can see already the progress I think—

Dr. Mignot: Oh, yes.

Julie: —in how far we've come. So that's gotta be the exciting thing is that we can see that that'll happen, even more so. Let's hope.

Dr. Mignot: Yes. The other thing that I think we need to make progress in, which I'm hoping is, recognition of narcolepsy. I mean there are still people who definitely have narcolepsy that don't know they have it. It's hard because— I don't know how to do it, you know a lot of people have done campaigns— I think we have to go straight to the public, so I really appreciate a little bit what— also what you are doing, by the way, of course, Julie. Because I think the new model shouldn't be to just get doctors to better recognize narcolepsy. I mean, this is hopeless. I mean most of the patients that come to me, very often it's not the doctor, it's themselves that figure out what it was. I mean it's a different world out there. But still, even with that there are still people who just don't know they have narcolepsy. And I just think we need to figure out— especially in children. I think it's really a problem, because children, if we don't catch their disease very quickly— it's so much harder to bring them back where they were. When they get out of the road, you know like, miles away— you have to bring them back. And— it's almost criminal, you know, if you don't treat the child really well from the beginning.

Julie: We're just so thankful to you Dr. Mignot, for taking this time.

Dr. Mignot: I hope it was helpful.

Julie: Oh, it's just so unbelievably helpful, I think. Alright—

Dr. Mignot: Thank you so much Julie, it was wonderful. As usual.

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