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SPEAKER 1: From the campus of Harvard Medical School this is *Think Research* a podcast devoted to the stories behind clinical research. I'm [? Abi. ?]

SPEAKER 2: And I'm Brendan and we are your hosts. *Think Research* is brought to you by Harvard Catalyst, Harvard University's clinical and translational science center.

SPEAKER 1: And by NCATS, the National Center for Advancing Translational Sciences.

SPEAKER 2: The COVID-19 pandemic has changed the way research is conducted. Many scientists have pivoted their focus to the virus, while others have been forced to work remotely or put experiments on hold. Having long been interested in sleep and dreaming, Dr. Janet Mullington's research looks at the many physiological and neurobehavioral effects of sleep deprivation.

As she began the fifth year of a behavioral intervention study for sleep and blood pressure in March of 2020, Dr. Mullington had to adapt to new circumstances and their effects on subjects in the study. Dr. Janet Mullington is the program director of the Clinical Research Center at Beth Israel Deaconess Medical Center, and an associate professor of neurology at Harvard Medical School. So Dr. Mullington, thank you for joining us. Welcome to the show.

JANET MULLINGTON: Thank you very much. It's a pleasure to be here.

SPEAKER 2: You're conducting a sleep study now. Just give us a little bit of background on this study that is currently being conducted.

JANET MULLINGTON: Our group looks at the effects of sleep loss on different physiological systems. We've been investigating the effects of insufficient sleep on different physiological parameters. We look at the effects of insufficient sleep on stress and autonomic response systems.

We're interested in the effects of acute total sleep deprivation. So acute sleep deprivation may be completely staying awake for 24 hours or 48 hours, or we've actually looked up to 88 hours of consistent wakefulness. People are actually pretty able to do this. Sometimes people will have micro sleeps within that time, but we actually record the EEG, and we're able to detect when people are falling asleep. And we've quantified--

SPEAKER 2: OK. So this is all done in a-- it's all done in a controlled environment?

JANET MULLINGTON: That's right. We bring people into a laboratory setting. We instrument the EEG and other physiological measures that we may be acquiring. We typically look also at hormones and inflammatory mediators. So inflammatory mediators include these interleukins. We analyze these proteins associated with inflammatory responses of the immune system.

We look at these and how they change through sleep deprivation, and we've seen that, when you deprive people of sleep acutely-- that is, a period of time where you don't allow them to sleep at all-- there's kind of a stress response-- a physiological stress response. And this is associated with an increase in blood pressure.

So blood pressure goes up, and these inflammatory mediators also go up. The inflammatory mediators are produced by white blood cells, and circulations are produced by the endothelial cells. In the monocytes and macrophages, they will produce these inflammatory mediators.

And they are indexed, if you will, or-- C-reactive protein is an indicator. That's something that we can measure pretty easily in the blood. And actually, when you send a blood sample to any lab, they can do the white blood cell counts for you and they can look at the-- they can quantify the C-reactive protein for you.

And the C-reactive protein is like a marker of host response. But these other proteins that are produced by the cells in response to an immune challenge-- they can be measured in the laboratory, and we also see that their production by these white blood cells is increased when people don't get to sleep enough.

So what we're seeing is that these inflammatory mediators, these proteins that actually tell the body to get into a defensive stance, if you will, are showing an increase. So this is a kind of physiological and immune stress that is activated when people don't get enough sleep.

SPEAKER 2: So that can affect a lot of different body systems. But what you're looking at in the study that you're conducting now is hypertension, or high blood pressure. And you actually were conducting this study when the stay-at-home order was instituted in Massachusetts. I want to talk about how your study was affected by the pandemic and the stay-at-home order, but could you just briefly give us the details of the study?

JANET MULLINGTON: Sure. So the study that we were working on when research was shut down due to the pandemic was an interventional study that was-- a behavioral intervention study. And it was designed to test whether improving sleep through behavioral interventions would help to reduce blood pressure.

Because as I said, we saw that blood pressure was increased. Inflammation was increased in acute total sleep deprivation. After that research, we had gone on to do other studies that found that, if you had three nights with only having half of your sleep in a row-- which many of us go through-- then you recover sleep, and then you go back to that same situation of insufficient sleep for three nights, go back again, this repeated cycles of insufficient sleep followed even by a night of recovery sleep still led to this pattern of increased blood pressure and some increased signs of inflammation.

SPEAKER 2: OK, so that was the work that led you to want to test this again and test it for the--

JANET MULLINGTON: Right. We thought, OK, there's this relationship-- or regulatory relationship between sleep and autonomic function, sleep and blood pressure. Can we use improving sleep to improve blood pressure? And so that's a very simple concept that we tried to translate into an intervention, and we have two behavioral treatments that we're testing now.

We believe they both may be effective. They both involve sleep-- very simple sleep hygiene principles. So obviously, we don't want people to be exposed to blue light, which can suppress melatonin and affect-- and be more alerting before sleep, rather than allow you to calm down and get to sleep. So we control that.

We control caffeine intake-- so no caffeine after the morning. And then we also control the regularity of your bed period. We know that it is helpful for your circadian rhythm to go to bed at the same time and get up at the same time, pretty much-- not to have too much irregularity in the timing and placement of your major bed period, which is, for most of us, at night.

So having a consistent bedtime and wake time is also part of the behavioral interventions. And in one intervention, we give a bit more sleep, and in the other, we focus on stabilization. So these, we think, both may be effective in lowering blood pressure, and we're testing to see which is better, if any of them is better.

We're using what we call a waitlist control. So we have three evaluations, where we have people come in for about 30 hours and they have [INAUDIBLE] blood pressure. They wear finger cuffs. We actually do this through the fingers, the digits, so that we don't have an arm cuff inflating and potentially disrupting their sleep.

We record their EEG, we take blood a couple of times a day, we collect urine to look at sodium excretion, and we also evaluate their cognitive performance and their mood and well-being self-reported indices. So we do this three times. We have the first command, do a kind of baseline adaptation day, where we get our baseline measures.

Then we have them come back again, and this allows us to have a second baseline look at them, because where-- we want to have two baselines, essentially because we think that it might be possible that just coming into a study has an effect on you.

We know that there's placebo effects all over, and this gives us an additional control, but it also allows them to adapt to our conditions, our measurement, the laboratory setting so that they're more comfortable on the second and third time they come.

So the second time they come is really our true or more true baseline, if you will, and then they are randomized to one of those behavioral conditions I described. And they go home and they're keeping that intervention for eight weeks before coming back. And we re-evaluate at that time to see if there's any decrease change in the blood pressure.

And all the way through this, from the first time we encounter them, we give them an [INAUDIBLE], which is a wrist-worn device that helps us to measure their sleep/wake activity levels and exposure. It actually allows us to monitor exposure to light as well. And we can use this in conjunction with an online sleep log that we give them.

So they write in their time to bed, and their time to wake up, and number of other things we ask them about their day throughout, and this lets us look at change through time. So we can look at that first period and see, is there any effect-- any sort of Heisenberg effect here? You come into a sleep study, and all of a sudden, you focus on your sleep?

So this, between the first and second time we evaluate them allows us to look at the effects of just coming into the study. And then, when they're randomized [INAUDIBLE] condition, we can look-- also, again, keeping the [INAUDIBLE] and the sleep logs-- look again how they adapt over time to their schedule. And then we evaluate when they come back. With the more intensive physiological and cognitive testing.

SPEAKER 2: So you're in your fifth year of the study.

JANET MULLINGTON: Just starting our fifth year-- that's right. So in our fourth year of this very big study, we had three participants who were already randomized to their intervention. When all research was suspended, we said, OK, what we decided as a study team to do, if the study participants were willing, was to have them just continue.

And three participants-- we asked them, OK, keep on your schedule-- because they were already randomized to the intervention. And so one of them actually had a medical family emergency, so actually had to stop, but the other two kept their schedule. And now we're waiting to have them come back into the clinical research center to complete that study.

So they will actually be more case-- of case study participants to see how the effect of keeping this now for an extra three months of intervention, or four months of intervention might look. But everything was stopped, and we have other people who are waiting to come in for a visit 2, where they get randomized a condition-- and visit 1.

So we were stopped in mid-flight, if you will, and had like a dozen participants who were at different stages of this study. So now we are going to restart and bring them in as soon as we can to complete.

SPEAKER 2: When we spoke last week, you were talking about how your lab-- the physical space adapted, and there was a lot of working together with different groups in the hospital. Could you tell us a little bit about just the changes in the physical space that happened?

JANET MULLINGTON: Well, when COVID hit, the hospital assembled a team to find a way to accommodate and expand our inpatient capacity, our ICU capacity. And so there was a lot of rapid change and reallocation of resources in order to meet the needs of the COVID patients.

The institution needed a place to provide a safe space, if you will, for patients who had blood cancer-- cancers, who needed to-- who thought that they might have COVID, and needed to have a place to come and get screened for COVID. So they asked if they could borrow our Clinical Research Center.

And we still, of course, had to do some research protocols that were ongoing that were what we call life essential protocols, that needed to be moved to-- that needed to continue during the pandemic. So we set up a satellite.

Within the span of a week, we turned our clinical research center into a COVID safe space testing unit for these oncology patients, and then we took over another space in another building for a satellite clinical research center-- set up a lab-- a wet lab there so that we could do the blood processing and do the other research protocols that were life essential, undisturbed by everything else that was going on in the hospital.

So that I was doing in my role. I was participating in those changes in my role of Clinical Research Center program director. But also this was impacting my own research, which had to go into suspension with the majority of other research that was going on at our institution.

SPEAKER 2: Right. So you're the program director for the research center, and then you're also conducting your own study-- so having a balance both of those things and those--

JANET MULLINGTON: Right.

SPEAKER 2: --competing priorities.

JANET MULLINGTON: Well, they align pretty well. Yes, because the role in the clinical research center is really helping investigators access the resources they need to do their research. And Clinical Research Center is a-- it's really a shared facility. So we have investigators from all around the institution from different departments.

We have close to 100 investigators-- early career investigators to more senior investigators-- who use the resources of the CRC. So it's a shared model, and it also-- so it allows kind of a flexibility. It's a core model that allows the flexibility so that, when you need the resources, they're there. You can you can tap into the resources that are there for a fee to your grant.

And then, when you don't need those resources, you're not paying to support as many staff. So it's a good model. It works well, and it also provides the opportunity to be more efficient with space use and-- because people share the space. You're not working. You don't need to have a complete laboratory of clinical space for yourself.

You share it and book into it with others, and it also allows early career investigators to come together and meet each other on the floor. It's a facility that allows sharing of certain equipment that cuts across areas.

Just give you an example of sleep, we have investigators in neurology who do sleep research, in psychiatry, in pulmonary medicine, in cardiology. All of these different systems, there's-- everybody sleeps, and sleep affects a multitude of physiological and systems that contribute to disease in different ways.

So that's easy to share space and equipment so that EEG, the [INAUDIBLE] is used by these different groups, and blood pressure, and blood drawing is common to those protocols. Also, with regards to another area is a movement-- the study of kinetics and body movement. We have a lab that is used by neurology for movement also by orthopedic researchers. So there's opportunities for investigators to come together and interact with other investigators in different fields.

SPEAKER 2: Right. OK. That's really interesting. Yeah, because a cardiologist who wants to study sleep doesn't have to set up their entire own sleep lab.

JANET MULLINGTON: Exactly.

SPEAKER 2: They can just call you and book the time. That's great. So when you were talking about that sharing space and people coming together on the floor, now in the post-COVID era, it's-- these ideas of sharing space, and sharing equipment, and-- that's all very tenuous, and people are very reluctant to share space. So how does this new era we're living in-- how is that affecting how you think about the research center, and how is it affecting how you're starting-- as you restart your study, what kind of changes are you putting in place?

JANET MULLINGTON: That's a very good question. It's right now in the early stages. We have begun to in clinical research again. In our Clinical Research Center, we have to plan carefully the scheduling of studies. We have to have adequate PPE. And we need adequate space, so we don't want to have crowding in rooms.

And this is practically a very challenging thing when you can have-- so we had initially started with 150 square feet. If you think of giving people-- a 6 to 10-foot spacing apart from one another. We were trying to plan for 150 square feet per person.

And this is very difficult to conduct research when you're at a distance. Sometimes you have to-- just as in the clinical care situation, you have to get close to the participant in order to carry out the research measures. So we are using PPE, and the participants are using PPE, and we're minimizing the amount of time that's spent face to face.

It's actually provided the opportunity for us to think about ways to do remote signing of informed consent. So anytime a participant engages in a research project, they have to have the study fully explained to them, and they need to sign a document that they are consenting to participate in research.

And so this requires that the somebody who's qualified on an investigator team explains and spends the time with that participant answering any questions that they have, and making sure that they fully understand what they are committing to participate in.

So this used to be done face to face for the whole thing, and now we are developing ways-- so we have our red cap signature, or the FDA now has an app that you can-- that can be used for FDA trials. There are ways that people are working to develop to sign the informed consent without having to use paper and pen. And so that's being done remotely.

So the consenting is being done remotely and the signatures are being done remotely, where it's possible. And we can even have the-- some of the screening steps or some of the intervention steps can be done remotely. So we're, as much as possible, trying to think of, what's essential to get close to the participant in order to do, and what can you do without being in the same proximity, without being within that 6 to 10 feet of that individual?

What can you do through the technology that now have available to us. So even telemedicine then-- if you're wanting to do a history or interview the patient, you can do a lot with the telemedicine techniques. There's still parts that can be done. You still have to take somebody's blood pressure by getting close to them. You still have to get close to them for their temperature and vital signs, measuring the weight, and so on.

SPEAKER 2: People are still doing that 30-hour sleep in the lab?

JANET MULLINGTON: Now now, but they will be-- yes. And so for example, with my study, we will move to sign the informed consent through this REDCap e-signature. And we will explain the study. We'll have to move some pieces of it that we used to do. Instead of four visits, we'll try and accomplish the same thing with three visits.

So we'll send people a blood pressure cuff to their home, and we will send them their ActoGraph to their home. I was describing how we give people an ActoGraph as soon as they come into the study, and they keep it through those three visits of this study.

Well, now we will send it to them, and they will begin at home after we've done the informed consent and initial screening by remote methods. We will have them come in, and we'll move-- instead of doing their screening blood pressure in the CRC, we will have them do it at home with the remote blood pressure cuff that we send them, and take the information in.

And then we'll verify it when they come in for their first overnight stay. So we're thinking about ways that we can do more at home, and less with direct face to face. And all those studies they're doing this-- finding ways that they can reduce the amount of up-close time, but still using PPE-- conduct safe research visits.

SPEAKER 2: When did you think, OK, we might shut things down? What was going through your mind when you were making that decision? Was it kind of a group decision, where you were talking to different people different program directors?

JANET MULLINGTON: It became parents very quickly-- I think, that in mid-March, things had really come to a head, and it was quickly apparent that research was going to have to be suspended, and that only the research that would be harmful to a participant to stop-- so that life essential kind of research would continue.

That occurred over a fairly short period of time. I think, just within the first couple of weeks of March, things changed very, very rapidly. And the hospital very quickly set up a command central kind of emergency response team that discussed and looked at the data that was coming through, and actually had a whole network of hospital leadership discussing, OK, what should we do, and how can we gear up and make sure that the hospital is ready to take care of the patients?

So that occurred from a clinical leadership perspective, and the clinical research really looked to their leadership to tell us when we had to suspend. And of course, we did immediately, but it was it was very rapid in transition.

SPEAKER 2: Did you even have a moment to stop and think, or it was just [INAUDIBLE] things were moving so quickly, you just were going with it?

JANET MULLINGTON: Well, I think that it's fair to say that there were a few days where we were wondering whether we could continue safely. Were there things we can do? But if you recall, we were-- people weren't even wearing masks routinely. And initially, in March, they were-- the CDC wasn't recommending masks.

And now we're in a very, very different place. We understand a lot better how to protect ourselves. So I think that it's appropriate, now that the research can proceed in a careful and safe way of using PPE, and making sure we have adequate space, not overcrowding any of the space.

So the research will start up more slowly. We will be able to do less with the space we have for a while, but I think it is time to begin again. But when it first transpired, it was a very rapid realization that everything had to stop. And there was some discussion for just a couple of days on what exactly would be able to go on.

And I think that the institutions were very supportive of one another, and shared all of their protocols and information, and discussed really in a collaborative way how to proceed, and I think did a superb job. The research has been suspended all across the country. The first priority has to be the safety of the patients, of course, in clinical research, and so I think the right decisions were made, and were made very quickly, in fact.

Now, though, to begin research again, we have to understand it'll take time. And I think that the sponsors are all very understanding and supportive of this. Nobody wants to cause undue risk. It's going to be challenging for a great many protocols to get caught up, and I think many protocols will not catch up to their targets.

And I think there will have to be an understanding. This is an unprecedented time for society, but for research, it's no exception. And we'll have to make the best and do our best to get caught up, but we have to do it in a safe way.

SPEAKER 2: Dr. Mullington, thank you very much. It was a pleasure to have this conversation with you.

JANET MULLINGTON: Thank you very much, Brendan. It was really nice to have a chance to talk with you, and good luck with your future endeavors.

SPEAKER 2: Thank you for listening. If you've enjoyed this podcast, please rate us on iTunes and help us spread the word about the amazing research taking place across the Harvard community.

SPEAKER 1: To learn more about the guests on this episode, visit our website, catalyst.harvard.edu/thinkresearch.