

Russell Foster:

In depression, for example, what tends to happen is that sleep and circadian rhythms are disrupted prior to a depressive episode. It's a very good predictor of impending poor mental health, and it's also been demonstrated that sleep and circadian rhythm disruption in middle years can be a risk factor for dementia in later years.

LuAnn Heinen:

That's Professor Russell Foster, head of the Nuffield Laboratory of Ophthalmology and director of the Sleep and Circadian Neuroscience Institute at the University of Oxford. His career has been dedicated to deepening our understanding of sleep and 24-hour circadian rhythms, applying this knowledge to improve health and quality of life. His research findings and their implications are shared in his book, *Life Time: The New Science of the Body Clock, and How It Can Revolutionize Your Sleep and Health*.

I'm LuAnn Heinen, and this is the Business Group on Health podcast, conversations with experts on the most relevant health and well-being issues facing employers.

Today, Russell Foster and I have a wide-ranging conversation about circadian rhythms, including how the timing of when we eat, exercise and take medication can change health outcomes, and factors that influence circadian rhythms for better or worse, and the implications of this field of research for us all, including medical professionals and the public.

Today's episode is sponsored by DayTwo, a precision nutrition solution using the world's most advanced proprietary microbiome science. Leveraging food as medicine to improve metabolic conditions and overall health, DayTwo uses an individual's gut microbiome data to predict blood sugar response and assign a personalized score for each food before the first bite, helping make small adjustments with big results.

Russell, welcome to Business Group on Health podcast.

Russell Foster:

I'm absolutely delighted to join you. LuAnn.

LuAnn Heinen:

Sleep is very much on people's radar. People pay attention to it as a health and well-being priority. We track it. We worry about quantity and quality. And the relationship between sleep and circadian rhythms isn't necessarily fully understood. We know circadian rhythms is a bit broader. What exactly are circadian rhythms?

Russell Foster:

Essentially you can think of circadian rhythms as an internal biological representation of a day. We genuinely have an internal clock with a period of around about 24 hours and we use this to adjust essentially every aspect of our biology. If you think about it, for our biology to function, we need the right stuff at the right concentration, delivered to the right tissues and organs at the right time of day. It's the circadian system that gives you this wonderful structure in both time, and of course, within the space of the body. Why do we need it? Well, we live in an incredibly complicated world. We're on a planet that revolves once every 24 hours. The response of essentially all life on the planet has to adapt to the huge changes in light intensity and temperature and all the rest of it. Many creatures have divided up the earth on the basis of being either day active or night active, and those are profoundly different states. So we have to have a very, very different biology to adapt to either consciousness, for us the wake state, or sleep, which is of course a profoundly different state and requires a different metabolism, a different level of brain activity in certain specific regions of the brain. It's the circadian system that gives you this timing.

LuAnn Heinen:

You've written a wonderful book on the subject and you've said that each of us needs to align or set our internal clock to the external world. How exactly would we do that?

Russell Foster:

Well, there are a number of ways. It's great having this clock, which is of course fine tuning our physiology and behavior to the very demands of the 24-hour day, but unless it's set to the external world, it's of no use whatsoever. Classic mismatch, of course with the internal and the external day, will be jet lag. I work closely with blind veterans in both the UK and the USA, and those individuals have no eyes or many of them have no eyes or very radical damage to the eye. Without the eye you can't detect the light-dark cycle. What happens is the clock just drifts off, and for most of us, about 90% of us, the clock would get later and later and later. We'd see this as getting up and going to bed around about 5 or 10 minutes later and later each day. What we need is daily exposure to the light-dark cycle, and that's the primary way in which the internal clock is set to the external world. Now, it's not the only factor. When we eat and when we exercise can also help entrain, regulate our circadian system, but light is by far the most important factor.

LuAnn Heinen:

I would vouch that most of us really are not thinking about setting our internal clock to the external world. We tend to think we've progressed. We as a modern society do what we want, whatever time we want. We work night shifts. We do travel across time zones, as you mentioned, without skipping a beat. We stay up till 2:00 a.m. on Saturday night and catch up on Sunday.

Russell Foster:

Yes, I think we are a supremely successful species in so many ways and that's because we have a profound sense of arrogance. We, as you rightly point out, feel that we can do whatever we want, whatever time we choose, and of course we can't. We are the product of tens of millions of years of evolution, and we can't just abandon that biological baggage and so we can't do what we want whenever we choose. We are bound by our internal clock, which of course is set to the external world.

LuAnn Heinen:

I think you've said that the amount of sleep we get is less critical than aligning our sleep to our circadian rhythm.

Russell Foster:

Well, yes and no. I mean, what I think is incredibly important is to appreciate that we are all remarkably variable. The sleep duration that we may need, depending on who you are, can be as little as six hours. Genuinely some people can manage on six hours, others need 10½ or maybe even 11. Certainly, when we're younger, we'll need much more than 10. In fact, when we're babies, of course, we may sleep 18-20 hours a day when we're first born. That changes as we age, but there's huge variability with sleep duration, but also sleep timing. Some of us are genuinely lax. We like to get up early and go to sleep early. Others are owls and we go to bed late and get up late. There's a biological basis to all of this, and this is called our chronotype - essentially what type of body clock, what type of circadian system we have. You can find out what type of body clock you have, what type of chronotype. There's a questionnaire in the back of the book, *Lifetime*, but there are lots of questionnaires you can also take online.

Our chronotype can be defined on the basis of three things. One is our genetics. We now know that there are tiny changes in some of the critical clock genes that can predispose us to want to be a morning type or a late type, or of course, an intermediate type. So by our genetics, our parents are still telling us what time to get up and go to bed. The second is our age. From about the age of 10, there's a tendency to want to go to bed later and later and later and this peaks in our late teens and early twenties. Men tend to peak later than women and tend to have on average a later chronotype. Then we'll move to a more morning chronotype as we age. By the time we get to our late fifties and early sixties, we're getting up and going to bed at about the time we got up when we were 10, 11, 12. And, significantly, that is about a two-hour difference. So somebody in their late teens, early twenties, will want to go to bed approximately two hours later than somebody in their late fifties and early sixties. That's a significant amount. So asking a teenager to get up at seven o'clock in the morning is a

bit like asking a 55-year-old to get up at five o'clock in the morning. That's the sort of impact. So there's a biological basis for that.

We've got our genes, we've got our development, and that's closely linked to changes in some of the puberty hormones, the sex steroids rising rapidly during those early years and then declining slowly as we age. But there's a third factor which determines our chronotype, which is when we see light. We said that light is critically important for setting the clock, but light has different effects at different times. So dusk light delays the clock, will make us get up later and go to sleep later, whereas morning light means that we'll get up earlier and go to bed earlier. When we were all agricultural workers, we were exposed to a symmetrical light-dark cycle. The delaying effects of light at dusk and the advancing effects of light at dawn would be sort of compensated, they would self-correct. But many of us now only sample part of the light-dark cycle. We live in dim, dark caves essentially. We did some studies a few years ago on university students all around the world and showed that the later the chronotype, the more owl-like they were, the less morning light they actually detected, which would advance their clock, make them get up earlier, and they got much more early evening and dusk light. So that shifted the clock to a later time. We have our genetics, we have how old we are, and when we get light exposure, and that all adds up to the type of sleep-wake timing that each of us will experience.

LuAnn Heinen:

Now I'm suddenly thinking, this is a bit of a segue, if you're partnered with someone of the opposite chronotype, what recommendation do you have?

Russell Foster:

Well, there's one study which I rather like suggesting that the longest surviving relationships are actually between morning types and evening types, which I think is interesting. Now, the cynic might suggest that's because they didn't see each other much. I don't hold to that. If you can accommodate the sleeping habits of your partner, and that may be very different, then all of the other sort of things that life throws at you, it shows you are a relaxed and flexible sort of person, so you can deal with it. There are issues, of course, about sharing your sleeping space with a partner. For example, if they snore and you can't accommodate the snoring or deal with the snoring with earplugs, then my strong recommendation is, if you can, find an alternate sleeping space, you'll be far less irritated with your partner. It's not the end of a relationship, as so many people say, I can't possibly sleep apart, it means that it's the end of our relationship. It's not. It's the beginning of a new one, because you can then be fresher, you can enjoy each other's company, you'll have a greater sense of humor, and of course, aristocrats and the very rich have had alternate sleeping spaces for hundreds and hundreds of years.

LuAnn Heinen:

Yes, we've all watched *The Crown*.

Russell Foster:

Indeed. Yes, exactly. Yes.

LuAnn Heinen:

What are some of the ways ignoring circadian rhythms may catch up with us? Many of us seem to be on that path.

Russell Foster:

Yes, and I think it's important, you touched on this earlier, but it's quite difficult to make a clear distinction between the impact of circadian rhythm disruption and sleep disruption. The two systems are very intertwined and we've done lots of interesting new stuff on that. In fact, for example, if you don't get very much sleep, that can actually desensitize the circadian system to light. There are lots and lots of reciprocal relationships. What we tend to use the term now is sleep and circadian rhythm disruption or SCRD. The consequences of SCRD are very wide ranging. We can think about the impact of SCRD on our emotional responses, and so we find

fluctuations in mood, irritability, increased levels of anxiety, loss of empathy. I think this is a very interesting one. We actually fail to pick up some of the social and emotional signals from other people, our partners or our work colleagues or our friends. Risk taking in impulsivity - you do stupid and unreflective things if you've got sleep and circadian rhythm disruption. Very interesting studies have emerged showing that the tired and circadian disrupted brain has what's called a negative salience, which means it remembers negative experiences but forgets the positive ones. So one's whole world view is biased and one's decision-making is biased by these recollections of negative rather than positive experiences. You can also slide into sort of stimulant use. If you're tired, you'll want to drive the waking day with excessive coffee, perhaps. Then, of course, you need to turn that off because caffeine in coffee has a long half-life, it hangs around in the body for quite some time and people will then use alcohol or sedatives to reverse those effects of the alerting effects of caffeine. And the problem is they are sedatives. They don't provide a biological mimic for sleep. In fact, they can disrupt some of the really important things going on within the brain whilst we sleep. There's some of the emotional things that can be affected.

LuAnn Heinen:

Well, let's just stop right there and recap, because that was huge. So emotional response, risk taking and impulsivity and remembering the negative and forgetting the positive. Those are the kinds of things that we might not realize in ourselves.

Russell Foster:

Well, I think that's a really good point, because the tired brain is often so tired it can't detect how tired it is, and we can delude ourselves to thinking that we're far better able to cope than we are. I mean, it's that classic risk-taking impulsivity, yes, I think I can make that red stoplight. Well, no, you can't and you wouldn't do it under normal circumstances, but if you've got SCRD, if you're chronically sleep deprived, then you're going to make those stupid and impulsive decisions.

LuAnn Heinen:

I know we're not through the list. What else?

Russell Foster:

Okay, we're not even halfway through. Let's now think about some of the cognitive responses. Overall, our ability to process information is impaired. Our ability to multi-task, and of course, that's what we humans are brilliant at under normal circumstances. We're flooded with lots of sorts of bits of information and we extract from that the most important and respond to it, so with all of the stuff coming in, we can make decisions. We fail to multi-task when we have SCRD. Memory consolidation, the failure to lay down facts and experiences that we've encountered during the day, but it's not just memory, it's also information processing. Some really wonderful studies have shown that proper sleep allows us to problem solve. I mean, our grandparents often said sleep on it, and many of us, I think, anecdotally can sort of remember waking up and having found the solution to a problem we've been thinking about. Our ability to process information goes very badly when we don't get the sleep that we need. Our communication skills, our decision-making skills, our creativity and productivity all decline and overall our social connectivity, our ability to act as a member of a group fails. So that's some of the cognitive responses and we, of course, just discussed the emotional responses, but the longer term impacts upon our physiology and health can be profound. A relatively short amount of sleep disruption can provide daytime sleepiness and micro naps. In the United States, it's been estimated between a 100,000 and 300,000 crashes on the freeway system are associated with falling asleep at the wheel and just falling asleep. There's a study in the UK on junior doctors showing that after the night shift, 57% of junior doctors had either had a crash or a near miss on the drive home. We show altered cardiovascular responses, higher rates of hypertension, for example, altered stress responses, we tend to be overly stressed, lowered immunity, high rates of cancer. I think this is really interesting. In fact, the World Health Organization has now said that night shift work is a probable carcinogen on the basis that long-term nurses and other individuals who are undertaking night shift work have higher rates of colorectal cancer, breast cancer, and some studies on airline pilots showed that there are higher rates of prostate cancer. I think that's something really very interesting and something rather sobering that we need to be aware of. Our metabolic systems can be

completely distorted, so higher rates really have much higher rates of type 2 diabetes and obesity in night shift workers and other groups who are chronically sleep deprived. Very importantly, our moods and depression and psychosis can be made much worse as a result of SCRD.

We've done quite a bit of work in this area, and a colleague of mine, Dan Freeman in psychiatry here in Oxford, looked at the impact of insomnia, really quite severe sleep disruption, on a range of psychiatric parameters, including one's cognitive abilities and one's levels of anxiety, and found that you could actually decrease these levels by improving sleep. We also know that in depression, for example, that what tends to happen is that sleep and circadian rhythms are disrupted prior to a depressive episode. It's a very good predictor of impending poor mental health. And just to complete the list, it's also been demonstrated that sleep and circadian rhythm disruption in middle years can be a risk factor for dementia in later years. This has been known for some time and now we have some mechanistic explanation. For example, there's a recently discovered brain filtering mechanism called the glymphatic system, and this will get rid of misfolded proteins called beta amyloid. Beta amyloid accumulation within the brain is associated with dementia and Alzheimer's. So whilst we sleep, we're actually getting rid of some of these misfolded and toxic proteins. I wouldn't say that poor sleep is going to cause dementia, but if you are sort of at risk of developing dementia, then poor sleep in the middle years could certainly be a risk factor.

LuAnn Heinen:

My goodness. Well, so how can people who are living in the modern world and have all of the sort of social pressures and work schedules that lead us to social jet lag that you referenced earlier, which is when our obligations and/or our recreation takes us away from our natural circadian rhythm and we may be out of touch with it, we can assess our own chronotype. What else can we do to understand if we're possibly in this state of sleep and circadian rhythm disruption and how to get out of it?

Russell Foster:

I think that's a critical point. Of course, we are so different that we need to take some ownership of this. How do you know if you're not getting enough sleep? Well, if you feel you can't perform optimally at your peak during the day, and I think we all get a sense of, yes, I'm really on fire today, I'm firing up on all cylinders, but if you oversleep extensively on free days, let's say the weekend or when you go away on holiday, that's a sign you're not getting enough sleep routinely. If you're dependent upon an alarm clock or somebody else to get you out of bed, you're not waking naturally, again, suggesting you're not getting the sleep you need. If you take a long time to wake up. If you've got sleep inertia, that's another sign you're feeling sleepy, irritable, and fatigued when you are awake. If you crave a nap during the day. If you find, again, you're doing overly impulsive and stupid things. If you're craving caffeinated and sugar rich drinks, that's all telling you you're not getting enough sleep. Also, we're very bad at this, we need to listen to our friends, families and work colleagues. If they say you're increasingly irritable, you don't seem to be as empathetic as you were, you seem to be more disinhibited, that can tell us that we're probably not getting the sleep that we need. As I say, there's huge individual variation. It changes as we age, but we must be tuned in to those sorts of issues.

LuAnn Heinen:

It is a little bit complicated for non-scientists to understand we have all these clocks in our body and it's not supported by most primary care physicians or the medical community. They haven't asked about sleep or let alone circadian rhythms, at least not in my experience.

Russell Foster:

Yes, I think that's absolutely right. I think there are a number of reasons for this. We're a relatively new field, and up until fairly recently, I mean after all the Nobel Prize was given to three researchers from the states who were the first to discover the molecular basis of the circadian rhythms, the clock, not in humans, but in a fruit fly. It was a phenomenal achievement, one of the great success stories in neuroscience over the past 100 years, but that was 2017. And certainly when I was going to meetings, we were 120 people maximum. Now we're thousands of people that attend our meetings. People will understand what is broadly meant by a circadian rhythm. I think it we're a new field. The medical curriculum, and I teach pre-medical students, is

crammed to bursting. Trying to get lots of education in this area is tricky because you're fighting with your colleagues who say the heart should get more lectures or the kidney or the gut or the brain, so you're fighting to squeeze the subject in. In a five-year pre-medical training, many medical students may get one or two lectures. That's it. And it won't be the sorts of things that we're talking about. It'll probably be about how the EEG, the electroencephalogram, changes with different stages of sleep, so it isn't directly mapping on to health. There's a lack of education. But I think the third area is when I talk to my family of medics, I sort of say, why aren't you paying more attention to drugs at specific times of day, chronic sleep deprivation, the importance of circadian rhythms? And they will respond that our health care professions are running as fast as they can to stay where they are, classic sort of red queen, and trying to just impose yet another layer upon the things they have to think about. Their brain is full in a sense and until we can really demonstrate the importance of circadian rhythms to individual health, I don't think they will pay attention, which is again why I wanted to write the book *Lifetime* to make it accessible so that patients will then ask their doctor, well, what time should I take my medication? Is there a time factor here? I'm chronically tired. Why is this? What can I do? That will encourage our medics to try and go into the literature and find out more about the extraordinary level of science we actually have describing the health state's circadian rhythms and sleep. I think we're doing catch-up is the short answer to all of this.

LuAnn Heinen:

This is the Business Group on Health podcast, and I'm speaking with Russell Foster, an expert on sleep and circadian rhythms. In the second half of the show, we'll talk about everyday implications of his work.

DayTwo

In the United States, 1 in 10 adults have type 2 diabetes and 1 in 3 adults are overweight. DayTwo believes that with the right knowledge about your personal biology, food can easily be used for meaningful and sustainable clinical impact. Using gut microbiome profiling and machine learning algorithms to predict blood sugar response to foods, DayTwo empowers members through an easy-to-use digital platform to make small, highly personalized tweaks to their nutrition plans. This garners significant results including weight loss, A1C reduction, improvement in energy levels and sleep quality and reduction or elimination of prescription medications. Instead of removing certain foods from an individual's diet altogether, DayTwo's proprietary algorithm suggests food combinations that are unique to the member's microbiome makeup, taking the stress out of food choices. To learn more, go to www.daytwo.com or email us at contact@daytwo.com.

LuAnn Heinen:

Picking up on your book and some practical information that's included therein, let's talk about timing and impact of exercise, eating, taking medications.

Russell Foster:

Yes, I think this is really interesting. We kick off with exercise. During the sleep state, we are mobilizing stored calories to keep our metabolism going and our life going. During wake, of course, we're taking calories in, because we're eating and we're burning those calories to sustain our metabolism. Our metabolism is fundamentally different during the sleep state and the wake state. One argument for exercise is that when you wake up, do some exercise before breakfast, because that's much more likely to burn off stored calories. If you want to lose weight, then burning off those stored calories can be good. The problem is that first thing in the morning, we're not great at exercise. The amount of power we can exert and the sort of energy we can commit is relatively low. Our ability to exercise increases throughout the day and it peaks late afternoon, early evening, that's when all the Olympic records tend to be set.

LuAnnHeinen:

Is that regardless of chronotype?

Russell Foster:

No, I was going to come to that. That's a really important point because if you're a morning chronotype, your athletic abilities will peak earlier in the day, and there's been some lovely studies on this. If you're a late

chronotype, they will peak late afternoon and early evening. We've selected really for people that can perform better later in the day in terms of their exercise.

LuAnn Heinen:

I think I cut you off. You were about to talk about records being set.

Russell Foster:

Yes, if you look at when the finals for the big races and the big sporting events, they tend to be always late afternoon, early evening because it's sort of known that that's when records are broken. And, of course, when people have big games, they want records to be broken, so that's when they have their finals late afternoon, early evening. The suggestion for exercise is that a short bout of exercise before breakfast can burn up some of those stored calories, but then exercise later in the day, late afternoon, early evening means you can exercise for longer and with greater power, so a longer bout of exercise later in the day. But you're quite right, depending upon your chronotype, what time that will be. I mean, if you're an extreme lark, then you'll be doing it sort of early afternoon rather than late afternoon or early evening.

LuAnn Heinen:

The bottom line is we're exercising twice a day.

Russell Foster:

Well, ideally yes, if you want to do it for longer with greater vigor, then you're going to do it before you go to bed. That's great, because what that will also do is burn off some of the stored calories that if you haven't used up will be laid to fat and to stored calories. It's good to get rid of those calories, if that is an issue for you. That's part of the issue. The other thing is that the circadian system is constantly gating our metabolism. For example, if you have the same level of glucose infusion, and some wonderful studies from Eve Van Cauter, University of Chicago, did this in healthy young males and showed that same levels of glucose in the morning, lunchtime and evening, those glucose levels will come down much faster in the morning and at lunchtime than if you consume a large glucose meal later in the day. Eating late in the day, high sugar meals has been associated with a greater chance of type 2 diabetes, because the metabolism isn't there to sort of get rid of this glucose, so you sort of then develop a glucose intolerance. So exercise two times in the day, short bout in the morning, and then a long bout later in the day. Make sure it's not too close to bedtime, because you don't want to increase core body temperature immediately before you go to bed, because that will mean it'll be more difficult to get off to sleep. Part of the process of going to sleep is a drop in core body temperature, and if you've done very rigorous exercise close to bedtime, you'll raise core body temperature, so be careful of that. For eating, try and concentrate your calories during the first half of the day and have a lighter end of the day.

Now, of course, that's what people used to do in medieval times. The main meal of the day was what we would call lunchtime. And it's because of course we sort of reorganized our work life, so instead of going home for lunch, as many people did, even my grandparents' generation, you lived and worked fairly close to where you lived and worked. Now, of course, with long commutes and having to spend one or two hours getting into work and then getting away from work and the demands of work, many people will have almost no breakfast, have maybe something light at lunchtime at their desk and then have the huge great calorie intake at the end of the day. Our bodies can't deal with it as effectively and that massive glucose and calorie intake at the end of the day is associated with a high chance of obesity and type 2 diabetes.

LuAnn Heinen:

Then there are the night eaters. When they can't sleep, get up and eat at night.

Russell Foster:

Absolutely. Of course, shortened sleep duration has been associated with greater chances of obesity. There seem to be several factors going on here. What's quite interesting, and again, work from the University of Chicago, has shown that, again, using healthy university students, if they were only given 4 hours a night to

sleep, then their hunger hormone went up, I think it was something like 27% ghrelin, the hunger hormone went up. The satiation hormone leptin went down by something like 17%. At the end of about a week, carbohydrate consumption had gone up by 35% to 40% and they were becoming glucose intolerant after that relatively short period of time. One of the problems is that if you are sleep deprived, you'll want to eat more, which is a big issue. Now, of course, if you are not sleeping, then you're active, and if you're active, you are more likely to be raiding the refrigerator. There's a double whammy here. If you're active, you're going to be up and likely to be eating and, of course, your whole metabolic axis is distorted by lack of sleep and you'll crave carbohydrates and particularly sugars.

LuAnn Heinen:

Well, let's move on to taking medication. It's flu season, flu and Covid vaccine season. Any advice on timing of that?

Russell Foster:

Yes, the data is still being fully collected, but if we extrapolate from the flu studies, so there was a very important study published back in 2016, and basically it looked at the time of day of immunization against the influenza virus, the vaccine against the H1N1 virus, and it looked at individuals, in this case roundabout 70 years of age. Now, individuals were either given the vaccine in the morning or in the late afternoon. If you look at the effect, the how effective the vaccine was at generating an antibody titer, then in the morning you got a titer of about 400, whereas in the afternoon the titer was 100. A huge difference on the basis of when you had your vaccination. I guess if we extrapolate from the flu studies, then morning vaccination is probably going to be more effective than afternoon vaccination. There are some studies that have been published suggesting that is indeed the case. That can be complicated though, because if you haven't slept immediately before or immediately after the vaccination, you can also hugely reduce its effectiveness. This, of course, is really important for our frontline staff. During Covid, they were being vaccinated, but they were probably chronically sleep deprived, and so their vaccination was far less effective than if they had a good night of rest. I think going forward and the next pandemic, we want to make sure our frontline staff, if at all possible, are rested immediately before and immediately after they get their vaccination. These are the frontline staff, these are the individuals who are going to be most likely to be exposed, so they need to be the most protected.

LuAnn Heinen:

Wow. Yeah, they really need those 400 times more antibodies.

Russell Foster:

Yes. If we think about cancer treatments, there's an early study, and it is fascinating why this hasn't gone into the mainstream, because here some of the data are absolutely clear. There was a study published way back in 1993 by Rivard and colleagues, and these are children with childhood leukemia, and they were given a cocktail of drugs either in the morning or in the late afternoon and early evening. They looked at long-term survival over I think it was about four or five years, and those that had evening chemotherapy had about a 70% survival. Those that had the morning chemotherapy, it dropped to 35% survival. This is a massive difference just on the basis of the time of day. Other studies, for example, have looked at ovarian cancer. Bill Hrushesky, again for the United States, has done some really exciting work in this area showing that two schedules, schedule A and schedule B, different times of giving of the chemo, and it looked at survival over five years. One schedule, one timing, had survival of 45%, another schedule at the same drug, different time, survival had dropped to 10%. So same drug, same concentration, different time, 45% survival versus 10% survival. This is huge.

LuAnn Heinen:

So dramatic.

Russell Foster:

Yes, it's breathtaking. I mean, this is a big effect. I suppose it goes back to your question, which is why isn't this becoming mainstream? I think the response is, look, it's difficult enough to schedule an individual to get their

chemo or their radiotherapy at whatever time. Now if we're going to have to do it at a particular time for a particular individual, this is just overwhelming for our health care services. I think the future here is potentially quite exciting, because we may be able to give the infusion of the chemo, not the radio, but the chemotherapy perhaps in the home environment at using timed pumps, which would then allow you to get the chemo when you actually needed it. I think a lot of people are now paying attention to developing the technology that will allow us to give drugs at the appropriate time.

We've talked about vaccination, we've talked about chemo, but I think another area where there seems to be some very interesting issues is in stroke. There's a 50% greater chance of having a stroke between 6:00 a.m. and 12 Noon compared to any other time of the day. That is this dangerous window of stroke, and because it's so tightly timed, you can say, well, hang on, what can I do to reduce my chances of stroke? The strategy has been that many antihypertensives last in the body for quite some time, so by taking an antihypertensive before you go to bed, the antihypertensive is still around by that 6:00 a.m. to 12 Noon danger window. As the circadian system drives up blood pressure, then the antihypertensive can counteract that. There's strong data suggesting that after 10 years, taking your antihypertensive at bedtime versus taking antihypertensive first thing in the morning, there was a drop in death rate of 50%, which is again huge. I think everybody would think, well, the danger zone is between 6:00 a.m. and 12 Noon, so you should take your antihypertensive first thing in the morning when you wake up. The trouble is you are already halfway through the danger window and by the time the drug has been absorbed and then kicks in, you are actually past the danger window. It sort of makes sense. We're beginning to learn that different drugs at different times are going to have a really big effect.

LuAnn Heinen:

Is this starting to take hold? Are there antihypertensives labeled for suggested evening dose or physicians or the NHS adopting policies like that?

Russell Foster:

There are no clear policies at the moment. The advice will vary between different GPs. You may get completely differing advice. There is no standardization with this, so it's not there yet. Although, the literature is becoming fairly well-developed. One further really important aspect about this, which I sort of bang on a lot, is in drug development. What happens, of course, is that, and quite rightly, you test your drugs on mice and then you extrapolate to humans. But, of course, mice are nocturnal and we are diurnal. In one particular study, they gave a drug, which again was associated with recoveries from stroke rather than preventing stroke with an antihypertensive, this is people who'd had a stroke, and this was reducing damage, further damage to the brain. They induced a stroke in a mouse, gave the drug during the first part of the day, and it was fantastic. It was really effective. They then extrapolated that to humans and gave the drug to people who'd had a stroke during the first part of the day, and it didn't work at all. Then somebody realized that, of course, the beginning of the day for a mouse is when it's asleep and the beginning of the day for a human is when we wake up. They then said, okay, well if we give the drug then to the mouse at the beginning of the wake phase, what happens? Just like in humans, it didn't work. Here's a really good example where time of day is incredibly important, and we've got to extrapolate. We've got to compare like with like with when we extrapolate from our drug testing in mice to humans. It's been argued that maybe there are some incredibly valuable drugs that were invested in and developed over many, many years that failed when they went to human trials because they were given at the wrong time of day.

I think the drug companies may well be missing a trick. Now, what they'll say is, oh, no, no, no, what we do is develop drugs with a very, very long half-life so they will be around when the timed crisis occurs. But, of course, you then say, well, hang on, you're giving a drug at a higher concentration than you need for a longer time than you need to intersect with the timed issue. Of course, what that will do is increase the chances of side effects. And as anybody knows, if you go on one drug, you're often on other drugs to deal with the side effects. I don't think it's good enough to say, well, we just produce a drug with a long half-life. We've got to use precision drug taking to actually intersect with the circadian changes in health crises.

LuAnn Heinen:

Excellent. Yes, precision drug taking. Also, to your earlier point, precision medicine, it's a new meaning of precision medicine, if individuals can take their chemotherapy or their drugs consistent with their own chronotype, what's best for them.

Russell Foster:

Well, absolutely. I think for most of us it won't matter, but if you're a morning type, an extreme morning type or extreme evening type, then you should be able to adjust your chemo appropriately. But for all of us, we need to get certainly some chemo drugs at the right biological time.

LuAnn Heinen:

Let's talk a little bit about ideas for employers, particularly for those with shift workers, because you've suggested that there are things that could be done to alleviate some of the damage.

Russell Foster:

I think so. I mean, I think it will be absolutely absurd for me to say we shouldn't do night shift work and put the 24/7 genie back in its bottle. It's here to stay. But what we can do is develop interventions that will mitigate some of the side effects and some of the problems associated with driving our biology outside of its normal range as in night shift work. So, if we think about, and we've touched on some of these, the loss of vigilance on the drive home. Those junior doctors crashing into cars in the early hours of the morning, why aren't we downloading an app onto our smartphone, clipping it to the dashboard that can tell us if we're showing a head nod or the car is moving laterally and sets off an alarm, and of course, high-end cars are now having this technology built into it, so if you're falling asleep at the wheel, that's something we could do now.

The poor physical and mental health associated with night-shift work, we should be having higher frequency health checks to detect these problems before they become chronic. Higher rates of obesity, type 2 diabetes, metabolic abnormalities for night shift workers, well, what's the food available for these individuals? It's high fat, it's high sugar and vending machines full of sugar rich candy bars, and we should actually be giving a healthy food option to our night shift workers. Fast food is not the option here. It's going to make things much worse. To my knowledge, and I think there's a really good marketing opportunity here to develop a high protein, easy to digest snack for night shift workers, the healthy alternative when you're working through the night. The failure to appreciate the consequences of night shift work, both by the employee and the people they live with. It's worth pointing out that the divorce rate for night shift workers in some sectors can be six times higher than the same job during the day shift. And, of course, what happens is that as we discussed, you're driving your biology outside of its normal range. Your cognitive and emotional responses become decimated. Your partner thinks you've turned into a monster, and indeed you have. But that's the inevitable consequence of doing night shift work for most people. People need to be aware of this and I think, where possible, give people some slack. This is a really demanding job, and I think the partnerships need to appreciate that there will be changes in behavior and to accommodate that behavior where it's appropriate. Why don't we chronotype our workforce so the late types go on the late shift and the morning types go on the morning shift. What you want to avoid, of course, is a late type actually being put on the morning shift. At the moment, allocation is completely random. Now, it's not the whole answer, but it will actually mitigate some of the problems.

The other, I think, really important point is that some of the severe pathologies that we've talked about such as cancer, such as coronary heart disease, such as type 2 diabetes, develop over time. It may well be that we should limit night shift work to four or five years and then rotate people onto the day shift and then maybe back onto the night shift later on. The difficulty is, of course, finance. Most people don't want to do night shift work, but for economic reasons, they have to. I think this is a huge dilemma because many people with poor sleep are in a lower socioeconomic group. They have very little voice. They are the ones that are disproportionately affected. Not just adults, I might add. We did a study a few years ago on early teenagers and one of the questions we asked them was, do you share your sleeping space? Do you share your bedroom with anybody else, assuming there was going to be multiple occupancy of the bedroom. What we didn't ask is,

do you have a bed? What we discovered, and this is our appalling naivety, was that many children from a lower socioeconomic group don't have a bed. They're trying to sleep on the family sofa while the family are watching television late into the evening. These kids then go to school the next day, they can't make full advantage of their educational opportunities, and they're already being marginalized from society because of their poor sleep. I think that's something that we have been slow to recognize and we must pay some attention to.

LuAnn Heinen:

Absolutely. Yes, when you think of the TVs on all night and yes, the impact that's having on kids and adults.

Russell Foster:

But I don't want it all to be doom and gloom, because there are things we can do that we've talked about what an employer can do as a duty of care, I think, to help the workforce, but we can do things. Getting morning light, for example, making sure the clock is set for most of us, avoid excessive consumption of caffeinated drinks in the afternoon, which will keep us awake. I think critically that stepping back at the end of the day to relax. Reducing light levels, so it's not so much domestic light levels will shift the biological clock, but it will increase alertness and therefore delay sleep onset, so try and keep the levels low. Don't use alcohol as a sedative or indeed antihistamines. Try and avoid sleeping agents. Try and get into the right mindset whereby you can improve your sleep.

One thing, which I think is a real dilemma, and I sort of chuckle because of my personal circumstances, is that for many couples, the only time you get to really talk to each other is at the end of the day where you're lying in bed. Then of course subjects like family finances or whatever surface. So we've banned the discussion of anything stressful before we go to sleep, but I think that's actually something that's sensible. You timetable it, but it's not just before you go to sleep. The bedroom shouldn't be too warm. We touched on this earlier, that drop in core body temperature is important for sleep initiation, and if the bedroom is too hot, then that could be an issue. Of course, it's getting televisions, it's getting electronic media out of the bedroom being hugely difficult. Lockdown bedrooms became offices, and we haven't actually got rid of all of that work paraphernalia from our sleeping space. Ideally we should, if we can. Don't clock watch. Many of us may wake up in the middle of the night, and we'll come to that in a moment, and see an illuminated alarm clock and think, oh my goodness, I've only got two hours before the alarm goes off and then get all stressed and not then fall back to sleep again. My recommendation is don't have an illuminated alarm clock. An alarm clock, yes. It's important if you need an alarm clock, it goes off, but you don't need to know that it's two hours before it goes off. I think keeping a good bedtime routine, go to bed and get up ideally at the same time every day if you can.

We Brits, I have to say, I think we're not great at spending money on decent mattresses, beds and pillows. I'm not sure about the United States, but I do think we need to take our beds more seriously. 30% of our lives will be spent asleep in bed ideally. We need to indulge in something that helps us sleep and it's worth trying different things out. Go to the showrooms, try these things out. One thing that people tell me increasingly, it's defining the sleeping space very clearly, and you can do that using smell. Lavender, for example. Some people will have low levels of lavender because you go into the bedroom, think aha, and you associate that smell with sleep time, which I think can be quite useful. We've talked about earplugs. If your partner snores, it's worth bearing in mind that you need to make sure they don't have obstructive sleep apnea. You can tell that if they stop actually breathing for a while and then they start and they have these great big gasping intakes. If you detect what you think could be obstructive sleep apnea in a partner, they must get that sorted out. There are significant health problems otherwise. We talked about an alternate sleeping space. It's not a reflection on the quality of the relationship.

Finally, I would say that some beautiful work by Roger Ekirch has from historical records, and then Tom Wehr more recently in the lab have shown that the human sleep pattern is not a single uninterrupted 8-hour block, but it's being called either biphasic or polyphasic. Whereas you go to sleep, you may be asleep for an hour or so, you may wake up, you may become conscious that you've woken up or not, you go back to sleep again, and you may go through several of these sleep-wake cycles every night. The problem is that most people don't

know that that's the natural state. They'll wake up, think, oh my goodness, that's it. I might as well start drinking coffee and doing emails and get all stressed about it. Whereas, if you stay quiet, if you keep the lights low, you read a favorite few pages of your favorite novel, and then chances are you will fall back to sleep again. The key thing is not to get stressed.

LuAnn Heinen:

It's a great treat to have an Oxford University researcher who understands all the mice studies and can explain them so the rest of us can really benefit. I also really appreciated some of the wonderful quotes in your book. One of them, the Mahatma Gandhi, "the future depends on what you do today." I love that. I'd love for you to close us out by reading the last sentence of your book.

Russell Foster:

Okay, "the lives of both wise and foolish people all end in death, but the circadian wise will, on balance, live longer, be happier, and lead more fulfilled lives."

LuAnn Heinen:

Thank you so much for that, and thank you so much for being with us today. It was a great pleasure getting to know you.

Russell Foster:

The honor is mine. It's so exciting that you've wanted to take this subject seriously and engage with your listenership.

LuAnn Heinen:

I've been speaking with Professor Russell Foster, author of *Life Time: The New Science of the Body Clock, and How It Can Revolutionize Your Sleep and Health*. For more information on the fundamentals of sleep, hygiene and health, check out our 2022 podcast, *The Social and Emotional Tax of Sleep Loss*.

I'm LuAnn Heinen, and this podcast is produced by Business Group on Health, with Connected Social Media. You can help support the podcast by sharing with colleagues and leaving a review.