- Biological rhythms

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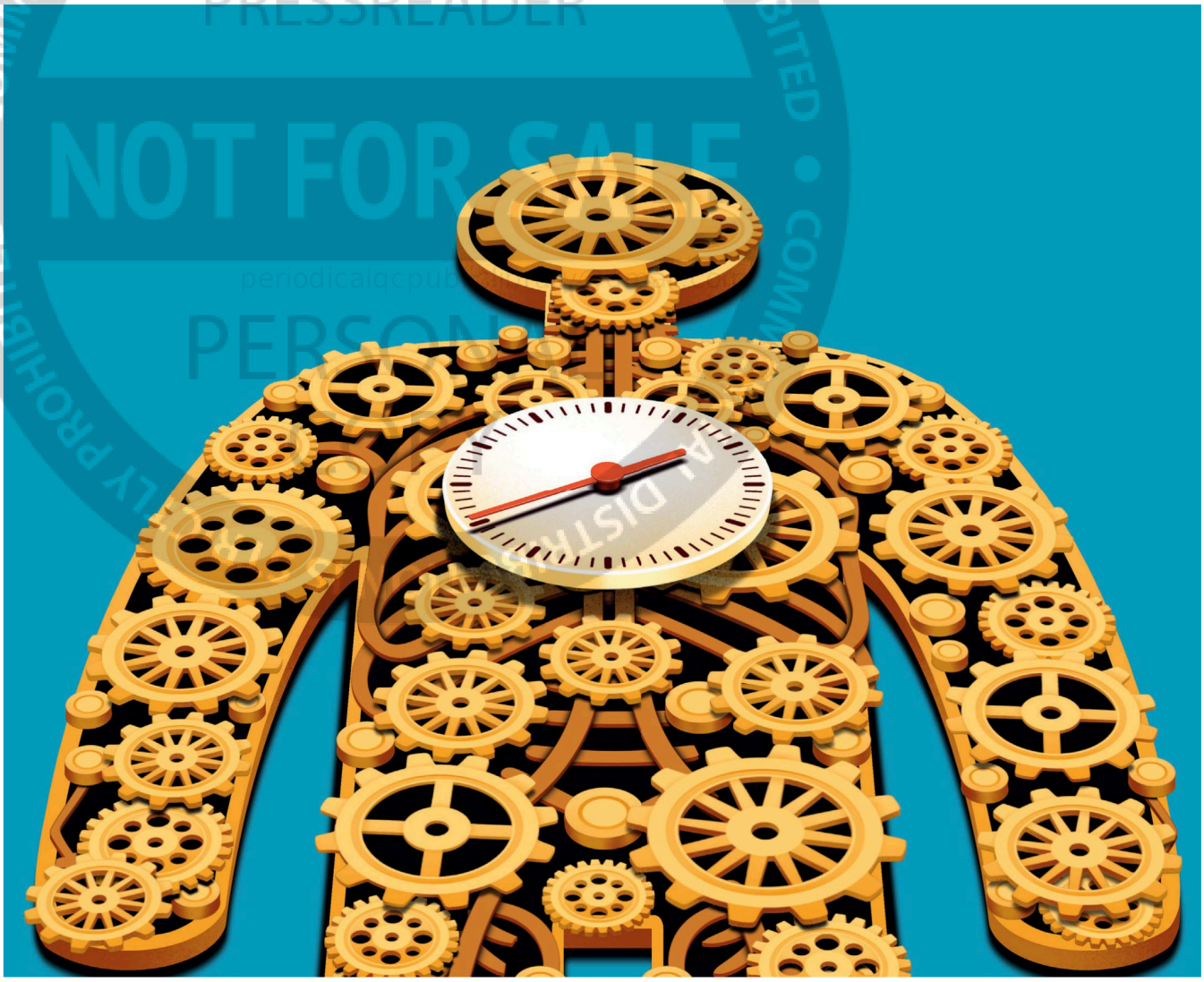
Features Cover story



NASH WEERASEKERA

Great timing

Understanding your circadian rhythm can supercharge your health. **Linda Geddes** tries the new tools for decoding your body clock

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SOME people check a wristwatch; others use a smartphone app, or the position of the sun. But although these methods will tell you what time it is, they won't reveal your internal time – that is, the timing of the clocks in your cells and tissues. This explains why I am standing in front of a mirror, plucking hairs from my head and plunging their bulbous roots into a small tube of buffer solution. Once the hairs have been analysed by a lab in Germany, I should discover what time it is inside my body.

For centuries, we have been missing a vital ingredient in health and medicine – the body clock. Over the past few decades, researchers have discovered that our mood, metabolism, athletic performance and cognitive capabilities vary over the 24-hour period, while a disrupted body clock is implicated in an ever-growing list of health conditions, from type 2 diabetes to cancer. It has also become clear that giving medications or interventions at different times of day can profoundly alter their efficacy and side effects, with more than half of drugs influenced by these time-of-day, or circadian, rhythms.

Yet, without a way to quickly and accurately read body clocks, our ability to capitalise on such insights is limited, which may even be harming us. A raft of tests now in development should change that, promising to help us understand our body clocks from a sample of saliva or blood, or even from hair cells like those I am sending to Germany. One of these tests is already on the market. Together, they could lead to a revolution in medicine.

Circadian rhythms are natural oscillations in the activity of our tissues that are driven by an internal clock – or rather trillions of clocks, ticking in every cell of our bodies.

"If you look at the expression of genes in different tissues, they're all doing different things at different times of day, and what those genes are doing depends on the timing of the clocks in that tissue," says Rosemary Braun at Northwestern University in Chicago.

"We have long been missing a vital ingredient in health – the body clock"

These clocks are controlled by a set of clock genes that produce daily fluctuations in a handful of clock proteins, and these influence the activity of numerous other genes in turn. Indeed, in 2014, researchers led by John Hogenesch at the University of Pennsylvania discovered that 43 per cent of mice genes are expressed rhythmically. Moreover, the study revealed that 56 of the 100 best-selling drugs in the US, and a similar proportion of the World Health Organization's essential medicines – the drugs that are supposed to be in every hospital in the world – target proteins whose rhythms fluctuate over 24 hours.

These results support the idea of chronotherapy – giving drugs at the time of day they are most likely to be effective and least likely to trigger side effects. Some clinical evidence backs the approach too, with cancer medicine leading the way.

Francis Lévi at Paris-Saclay University, France, became interested in the idea of biological rhythms through traditional Chinese medicine, which describes the vitality of different organs peaking at various times of day. He began to investigate this in the context of cancer, recognising that, whereas healthy cells usually only divide at certain times of day, cancer cells do so all the time. Because many chemotherapy drugs target rapidly dividing cells, he reasoned that giving these drugs when healthy cells are effectively asleep might allow larger doses to be delivered with fewer side effects. Initial experiments in mice confirmed this, followed by a small clinical trial in women with advanced ovarian cancer. Published in 1990, it suggested that side effects such as nausea and fatigue could be significantly reduced if the women received chemotherapy drugs at 6 am rather than at 6 pm.

Since then, Lévi and others have conducted further chronotherapy trials with other drugs, in various types of cancer. According to a 2022 review of 18 such trials, most showed evidence of reduced toxicity, while the efficacy of the drugs was maintained.

Similar results are now being reported in other fields of medicine. For example, the heart may be better able to withstand surgery in the afternoon compared with the morning, and the seasonal flu vaccine generates four times as many antibodies if given between 9 am and 11 am compared with 6 hours later.

"Not only is how the drugs hit their target influenced by the clock, but there's also evidence that how they enter the body and ›

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how they are excreted differs by time of day," says Robert Dallmann, director of the Patho-Physiological Molecular Clocks Lab at the University of Warwick, UK.

Even so, "there have been some studies that did not show the expected benefit", says Lévi. One explanation could be that each participant's internal clock is set slightly differently. "Until now, chronotherapy has adapted treatment to an average circadian rhythm in a population of people," he says. "But the timing of these rhythms can differ by up to 12 hours between patients."

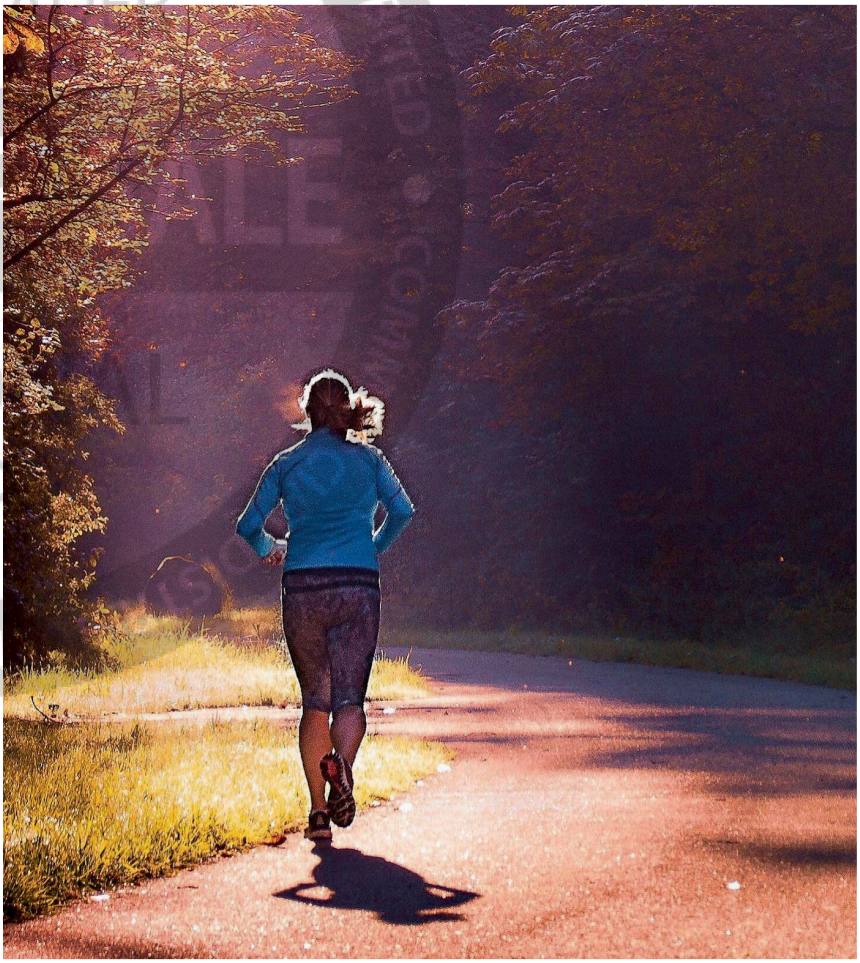
Perhaps then, chronotherapy isn't only about administering the right drug at the right time, but at the right time for each specific patient, says Angela Relógio at MSH Medical School Hamburg in Germany. "The problem is you need to be able to measure the [internal] time."

Until now, the gold standard for assessing internal time has been to record when individuals start to release a hormone called melatonin from their pituitary gland, which usually happens about 2 to 3 hours before they naturally fall asleep. This nightly event is controlled by a central body clock in the brain called the suprachiasmatic nucleus (SCN), whose job it is to keep the billions of clocks in our tissues synchronised with each other – and with the time of day outside (see "How to shift your internal clock", opposite).

Melatonin's release is thought to be one of these synchronising signals, helping the body transition into nighttime mode, so measuring the onset of this event is the metaphorical equivalent of listening for when a clock strikes midnight.

Useful as it is to measure this "dim-light melatonin onset", recording it is laborious. It requires blood or saliva samples to be taken every 30 minutes from late afternoon onwards, and because the release of melatonin is inhibited by bright light, the subject ideally needs to remain in a darkened room for the duration. The samples must then be sent to a laboratory for processing, so it can take days or weeks to find out someone's internal time.

This difficulty of telling internal time has hindered scientific progress in circadian medicine. However, researchers have been working on alternatives. Given that the products of clock genes – and the genes they regulate – fluctuate at different times of day, scientists have been searching for various proteins or other "biomarkers" in body fluids and tissues that could reliably



WIRESTOCK, INC./ALAMY

The intricate processes within your various body clocks dictate a preferred waking time

"The heart may be better able to withstand surgery in the afternoon"

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infer somebody's internal time.

For instance, Relógio is CEO of TimeTeller, a company that has developed a saliva-based test, while Hogenesch's team is investigating skin-based circadian biomarkers. Other research teams – including one led by Braun and others led by Derk-Jan Dijk at the University of Surrey, UK, and by Christopher Depner at the University of Utah in Salt Lake City – are developing blood-based biomarker tests.

For now, however, the only analysis available to consumers like me is BodyClock's hair test. For €199, it examines the relative amounts of messenger RNA – the genetic template for protein production – being expressed by clock genes in the subject's hair follicles at the time they were plucked from their head. Through comparison with when the resulting proteins are known to peak and trough in people on average, BodyClock's algorithm calculates how far advanced or delayed someone's internal clock is relative to this.

My test results suggest that I am an intermediate type, or "dove", and that my body begins to ramp up melatonin release at around 9.30 pm. Roughly 2 hours later, its concentration hits a level where my body switches to sleep mode, meaning I should naturally become tired at around midnight. This is when BodyClock recommends that I try to start sleeping, and I should try to wake up at around 8 am.

The company also suggests that my optimal eating time is between 8.30 am and 8.30 pm – or 6.30 pm if I am trying to lose weight, as my body is best equipped earlier in the day to convert food to energy, and not store it as fat (see "Eating with your body clock could improve your health", p 34). Meanwhile, the best time for me to exercise if I wish to optimise strength or endurance is between 5.30 pm and 7.30 pm. This is because body temperature, blood flow and blood pressure gradually increase during the day, contributing to improved muscle performance in the early evening.

As the author of a book on circadian rhythms, I didn't find any of this particularly surprising. It also fits with when I would naturally choose to go to bed and wake up, if not for the fact that I am forced to set my alarm clock to 7 am, to get my kids out of bed and off to school on weekdays.

However, I am not really BodyClock's target customer. Bert Maier, a chronobiologist at Charité – Universitätsmedizin in Berlin, Germany, who sits on the company's scientific advisory board, says most people who buy the test have sleep problems. "Some types of insomnia are related to a disrupted circadian clock, and in this case, we might help customers to readjust their clock or inform them what they should do to enhance or strengthen it."

The biomarker tests could also be useful in the context of clinical trials. Later this year, Lévi hopes to begin a chronotherapy trial that will see 242 people with non-small cell lung cancer receive immuno-chemotherapy. Although most will be randomly allocated to receive morning or afternoon treatment, a subgroup will have their internal rhythms assessed using TimeTeller's saliva test to see if personalising the timing of these drugs could further boost their efficacy.

In a recent trial, Lévi and his colleagues discovered that administering the treatment to people before 11.30 am was associated with a nearly twofold increase in overall survival from the cancer. "If we can double the survival of patients by treating them in the morning compared to the afternoon or evening, I'd expect that we should be able to at least further double this by personalising the time of administration," says Lévi.

Out of sync

There is a third way in which biomarker tests could be helpful. Over the past decade, evidence has been building of the harm circadian disruption can have on people's health, with links to psychiatric and neurological conditions, cancer, type 2 diabetes, obesity and cardiovascular disease. Such disruption occurs when our internal clocks fall out of sync with one another, perhaps because of shiftwork, inappropriately timed light exposure or social jet lag caused by inconsistent bedtimes.

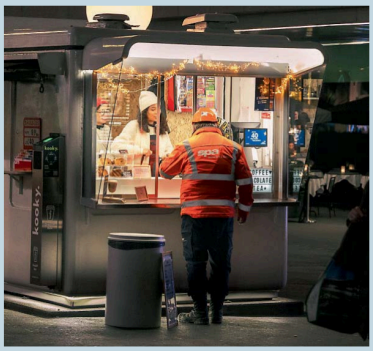
"Circadian misalignment is very strongly linked with many of the health issues of modern society," says Depner. "If we could measure biomarkers effectively, this would expand the populations that we can reach with our research. Most excitingly, we could use them on real-world shift workers to understand how their clocks are moving around with their different shift schedules. This could allow us to devise interventions ›

How to shift your internal clock

Our circadian rhythms are controlled by a small patch of brain tissue called the suprachiasmatic nucleus (SCN). Although its timing is regulated by a network of "clock genes", it is also influenced by our exposure to light, through conversations with a group of light-sensitive cells in the retina at the back of the eye.

When light hits these retinal cells, they send a signal to the SCN, altering the expression of its clock genes and tweaking its timing. The retinal cells are particularly responsive to light in the blue part of the spectrum, which includes daylight. Their effect on the circadian system is also strongly time-dependent. For instance, exposure to light in the early evening and at night delays our central body clock, meaning we feel sleepy later, while exposure to light shortly after dawn advances our clock and makes us more lark-like – early to bed, early to rise.

Melatonin supplements can also be used to tweak the timing of the SCN. To advance your clock (waking early and going to sleep earlier), you should take it roughly 4 to 6 hours before your normal bedtime. To delay your clock (go to bed and wake later), take it in the early morning, immediately after you wake up.



DIJANA ZULFIKARIC/ALAMY

Light exposure after dark can mess with your body clock

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to help mitigate the health risks."

For instance, researchers are exploring whether restricting when people eat, or the type of light they are exposed to during night shifts, could help to mitigate some of the detrimental health effects of shiftwork.

However, the tests that are currently available, or are being developed, are somewhat limited in what information they can provide, because samples must be sent to a laboratory for processing, rather than providing the results in real time.

For instance, BodyClock's hair test currently takes five weeks to deliver results to customers, which is a potential problem because our "chronotype" isn't entirely fixed, with the type and timing of light exposure being a major factor that can push or pull our internal clocks forwards and backwards. I previously conducted an experiment with Dijk that saw me cut out artificial light after dusk and expose myself to more natural light during the daytime. Doing so caused my body clock (as measured by my dim-light melatonin onset) to shift 2 hours earlier.

So, while BodyClock's results suggest my melatonin release significantly ramps up at 9.30 pm, this reflects my biology as it existed several weeks ago, which may not reflect my situation today, or five weeks from now.



PLAINPICTURE/SASKIA SANDROCK

Eating at certain times of day – in a pattern unique to you – could help with weight loss

Slightly out-of-date results may not matter if a doctor is simply trying to ascertain whether someone's insomnia is related to a significantly advanced or delayed clock, or in the context of a clinical trial. However, the ability to deliver more instantaneous results could be useful for shift workers who would like to adapt to a new shift pattern, or frequent travellers who want to overcome jet lag more quickly.

Say you had just flown from London to New York. "In the morning, you could pull a hair and run a test to find out the timing of your internal clock," says Dijk. "You could then use this information to help you overcome your jet lag through timed light exposure or taking a melatonin pill."

Getting it together

Another useful add-on would be if biomarker tests could assess the timings of individual organs, and how closely aligned they are. Although our body clocks gradually adjust themselves to altered patterns of light exposure caused by changing shifts at work or time zones, they do so at different rates, which can result in our gut rhythms falling out of synchrony with those of our brain, and so on. This ongoing desynchrony is suspected to be behind some of the adverse health effects that have been associated with shiftwork.

"If there are molecular markers that reflect what's going on in the liver, pancreas, muscle and all these other specific tissues, the question is: could we then use that information to try and devise interventions to help to better align them?" says Depner.

In other words, this first generation of body clock tests simply scratches the surface when it comes to reading the time inside us in a way that could usefully shape our lifestyles or improve healthcare. But researchers see the tests as a good start. If the past two decades have highlighted the importance of body clocks for human health, the hope is that the coming one will illuminate the cogs, levers and gears that we could pull to fine-tune their movements and keep all of us running on time. ▮



Linda Geddes is the author of *Chasing the Sun: The new science of sunlight and how it shapes our bodies and minds*

Eating with your body clock could improve your health

What if the timing of your meals mattered almost as much as what is on your plate? Mounting research suggests that our bodies may be primed to process food, especially carbohydrates, more efficiently in the morning compared with later in the day. Earlier on, our tissues are most sensitive to insulin, the hormone that helps to absorb sugar into cells.

Eating a large, carb-rich meal later in the day could lead to higher levels of glucose circulating in the blood, which, over time, could increase someone's risk of developing type 2 diabetes or metabolic syndrome, a group of health issues that puts you at risk of various conditions including this form of diabetes. Furthermore, we may burn slightly more calories digesting food in the morning. Several small studies indicate that evening snacks may reduce the amount of fat the body burns overnight, while eating earlier in the day boosts fat burning. While larger studies are needed to determine how such findings relate to fat storage and weight change in the wider population, it appears there is wisdom in the saying: "Eat breakfast like a king, lunch like a prince and dinner like a pauper."

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