Sleep 101

Sleep 101:
The Beginner's Guide to Unraveling the Mysteries of Life's Forgotten Third

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Acknowledgements

Urban legend has it that Pablo Picasso once was spotted, dining in Paris, sketching something on the check. An admirer, recognizing the great painter, approached him and asked if he could buy the drawing. To his delight, Picasso agreed to sell it. The guest, reaching for his wallet, asked how much he owed. The painter calmly asked for 200 000 Francs, a smaller fortune. The guest, obviously upset, exclaimed that it had only taken a few minutes to make it. Picasso shook his head and said “No *monsieur*, it has taken me all my life”.

This is the way my dad told me the story, so to what extent it is true I really can’t tell. However, although one can certainly come up with several take home messages and interpretations, I always thought of it as story about how all our accomplishments, big or small, are the product of a succession of innumerable events and encounters that we call our lives. And this humble attempt to share some insights I gained as a sleep medicine fellow at the University of Chicago is no exception. It would not have been or would have not been the same without the influence of more people than I have space to mention. That being said, I do want to extend my gratitude to a few individuals in particular.

Jamie, you are the love of my life and I hope at least one of your dreams now has come true. Mom, dad, Rebecca, thank you for everything, come see us more often. Daniel, sometimes all one needs is one good friend. Theo, hus 75, peppar, the dreams were sweet. Jan, we're not in Karlstad any more. Finally, many thanks to Babak, JJ, Hari, Sushmita, Amy, Hameeda and Raina for the discussions and laughs.

Introduction

It must have been sometime in August or September of 2008. I was having beer at McKeown's with John, a fellow alumni of KI (Karolinska Institutet, Stockholm, Sweden) who had joined me in New York for residency training. He was known in his program simply as Ken, due to his resemblance to the tall, blond boyfriend of Barbie. "Did you know that there is a fellowship in *sleep* medicine?" I didn't. "Apparently, you have an *amazing* lifestyle. You don't even have to come to work, you can read sleep studies from like…Hawaii! Talk about tropical medicine!" To two residents, putting in 80 hours a week, the prospect of making a living from the cool shades of a palm tree to the sounds of gentle pacific waves and a distant ukulele sounded like some unattainable fantasy. And as the contrast between this professional wet dream and a reality of q3 calls, impossible blood draws through inches of subcutaneous fat and of transporting the full spectrum of familiar and unacquainted body fluids to various labs became too painful, we soon dropped the subject.

The following day, apart from a slight headache, the thought of practicing sleep medicine still lingered in my mind. I had never really bought into the Honolulu gig, that just had to be too good to be true. But sleep medicine did exist. I googled it. And higher functions of the brain, such as thinking, creating and talking had always interested me. In fact to a point where I was spending evenings and weekends during med school studying the *Shaker* ion channel from fruit flies by expressing it in egg cells from frogs. This neuroscientific model is used to understand how human ion channels, which are critical to the brain and its complex functions, work. To my great excitement, while reading up on sleep medicine, I realized that the *Shaker* channel since my time in med school had been shown to be critical for sleep in the fruit fly. Consequently, the model I had used as a medical student should be valuable in the study of sleep biology!

Encouraged by what I took as an astrological sign, I decided to apply for a fellowship in sleep medicine. The functions of the brain, as mentioned, had always intrigued me. But sleep in particular was a different animal. The benefits of human communication, verbal or non-verbal are obvious. It is clearly an advantage to have the capacity to remember things. The ability to recognize a face or an object is evidently good to have. The benefit of spending a third of your life sleeping, however, left plenty of rooms for speculation in my mind. Why do we sleep? What is the evolutionary rationale for sleeping? What is sleep? I imagined myself untangling these questions interpreting currents from two-electrode clamped oocytes in the setting of a neuro lab at some Ivy league campus in a near future. Well, that didn't happen. At least not yet. But to my delight I was offered in the fall of 2009, a year after my encounter with Ken, a position as a sleep medicine fellow at the University of Chicago, the birthplace of this discipline.

I hope to share with you here the essence of the many intriguing and fascinating insights I gained into the phenomena we call sleep during that year. I hope you will find it as interesting as I have.

PART I

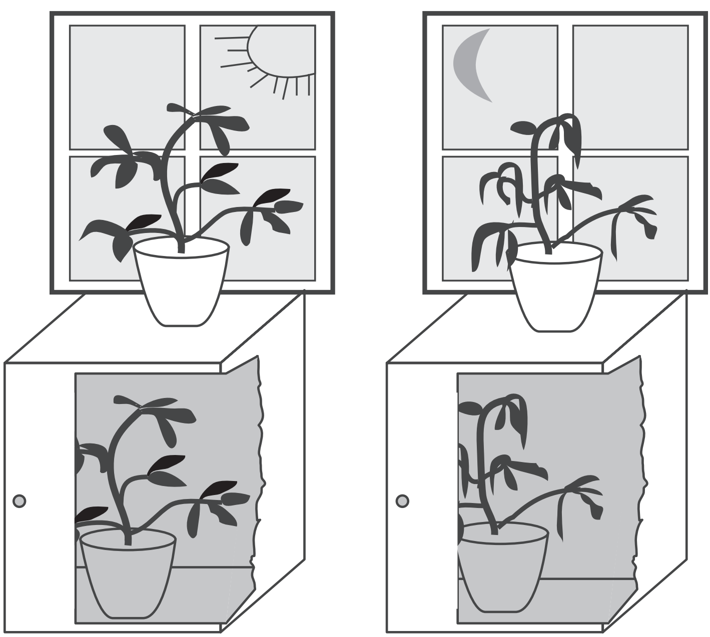
The rhythm of life

When you hear the word rhythm, the first thing that comes to mind may be humiliating attempts to master a latin dance form or the classic 90s techno hit "The rhythm of the night" by Corona rather than sleeping. However, although most commonly applied to sound, anything that happens in a regularly recurring fashion can be described as having a rhythm. The menstrual cycle is an example of infradian rhythms that occur over periods longer than a day. The contractions of your heart, in contrast, are an example of ultradian rhythms which have more than one cycle per day. If you, by the way, have noticed that at any given point one of your nostrils is more open and less congested than the other, you are not alone. This phenomenon is called nasal cycling and is another example of an ultradian rhythm. The nasal cycle is about 2.5 hours long. Some cycles are roughly, or circa, one day long and are thus called circadian rhythms.

The most commonly referred to circadian rhythm is the sleep-wake cycle. Although there is some variation between individuals, most of us sleep primarily nighttime and are awake and active during the day. As understanding what mechanisms control our sleep-wake cycle is key to understanding what makes us feel sleepy, why we get jet-lagged, why it is so difficult getting used to shift work and many other sleep related phenomena, we will spend some time discussing it.

On a historic side note, Jean-Jacques d'Ortous de Mairan (1678-1771) was a French scientist and is widely credited as having first described a circadian rhythm in the *Mimosa pudica.* As many other plant species, the leafs of this herb close during the night and re-open during the day. As plants need to absorb light for photosynthesis this is hardly surprising. However, what Jean-Jacques observed was that the *Mimosa pudica* maintained this pattern of opening and closing its leafs despite being confined in complete darkness (see figure below). This observation suggested that the opening of the leafs during daytime was not simply a response to light, but that the *Mimosa* knew what time it was.

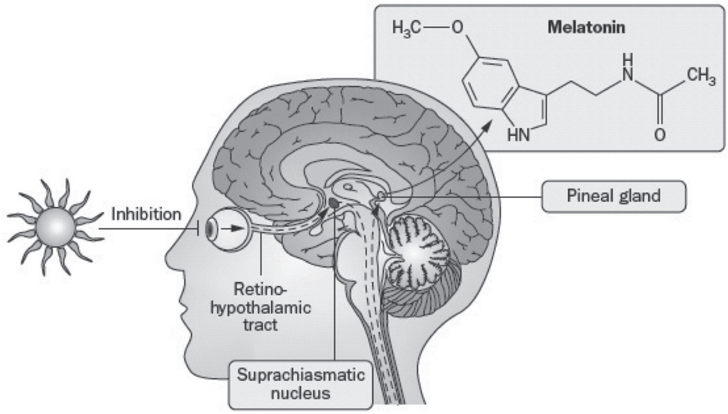
If you were asked at any given point what time it is, you could probably come up with a pretty good estimation without



looking at a watch. You would sort of just know or feel what time it is without having to make any effort. This may not seem very strange or surprising, but try asking yourself: How am I able to do that? You would probably answer that how bright it is outside and the position of the sun gives it away. Strong light and a sun in zenith indicate that it's about 12 noon. Dim light and a sun positioned low on the western horizon mean that it's about 8 pm. This is true, but not the whole truth. The sun is the most powerful and important indicator of what time it is. It is the main zeitgeber or time giver directly translated from German. The sun literally gives away what time it is, but there is more to it than that. If you think about it, you don't really need to see the sun to know what hour of day it is. After several hours in an artificially lit office or during a long commute underground you can *feel* the time. This phenomenon is not isolated to daytime. You may have woken up just before your alarm several days in a row or woken up in complete darkness knowing that it's about 3 am. What makes this possible is the second function of zeitgebers. A zeitgeber not only tells you what time it is at a given moment, but also acts as a reference point for that inner notion of time that we humans share with the *Mimosa pudica* and many other organisms, an internal clock. A biological timing device that each one of us consults on a daily basis. Most without even being aware of its existence.

Going back to the question of how we know what time it is at a given moment, we do that by exploiting environmental cues and by consulting our inner clock. In this chapter, we will explore the workings of this circadian timing device further. Let us start by looking at how it is set.

As mentioned, the main zeitgeber for the internal clock is sunlight. However, for the sun to be able to set your internal clock there needs to be a pathway for light to be relayed to the parts of the brain that are involved in circadian rhythms. Needless to say, such a pathway exists and is illustrated on the opposite page. The light that hits your eyes is transmitted via the oculomotor nerve to the pineal gland. The pineal gland is a pea sized endocrine organ located in the middle of the brain which



produces a hormone called melatonin. Melatonin is not produced all the time, rather the production of melatonin depends on the external environment. Melatonin levels are minimal during the day as production is inhibited by light. Towards the evening, as it gets darker outside and less light hits the eye, the inhibition of melatonin production decreases and the pineal gland makes more of it. Melatonin in its turn prepares our bodies for sleep by promoting sleepiness, lowering blood pressure and lowering heart rate. Furthermore, melatonin levels function as a biological signal conveying the time of the day.

Now, as the alert and intelligent reader you are, you might say: Wait a minute, how about people that live in perpetual darkness? Will they be constantly sleepy? Do they know what time it is at a given point? What happens to melatonin secretion? In fact people have lived in such conditions for generations. For example in Alaska, or in parts of my native Sweden, the sun does not rise for 3-4 months during the winter. Yet people there actually function pretty well and are relatively normal. This is where zeitgebers other than the sun come into play. Your 7 am alarm clock, that's a zeitgeber. Having lunch at 1 pm, that's a zeitgeber. Your kids coming home with the school bus at 4 pm, that's a zeitgeber. Watching the 11 am re-run of Dancing with the stars which you usually watch at 6 pm, in complete absence of other indicators of the time, that's just confusing.

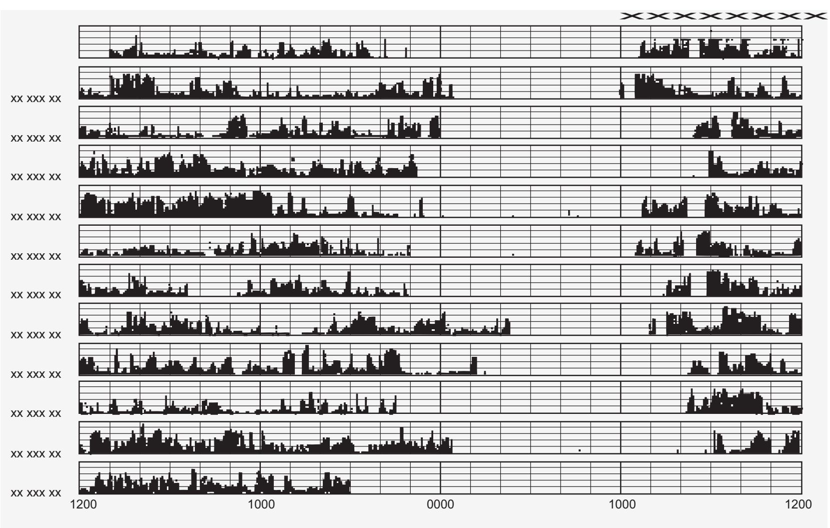
By setting their internal clocks according to these artificial zeitgebers, Alaskans and Swedes have a sense of what time it is and feel alert or sleepy at the appropriate hours. This may not seem very surprising; in contrast that is intuitively what you would expect right? But what about biological markers of time such as melatonin? Do they continue to rise and fall with the absence or presence of light or can they be manipulated with other zeitgebers? In fact, the latter has been shown to be true. Hormonal secretions are amenable to manipulation with artificial factors. For example, despite complete absence of light, melatonin secretion increases in Alaskans around 9 pm just as in Texans. And secretion of other hormones such as growth hormone or cortisol which typically occurs in early morning hours happens between 4 to 6 am in Danes as well as Ethiopians.

To re-iterate, not only can we change our habits to function in perpetual darkness, or light for that matter, but biological rhythms such as when we feel sleepy or at what time certain hormones are secreted can also be modified by manmade cues.

The value of knowing what time it is at a given point is easy to appreciate. And as we have discussed, we all have an internal clock which can tell us right of the bat, without consulting a watch or checking how light it is outside, approximately what time it is. However, a question you may be asking is: Shouldn't this internal clock be sufficient in itself to give us a sense of time? And consequently: Why do we need external cues?

It would surely not be impossible for whatever you believe created us, be that evolution, God or a giant turtle whose back the world is sitting on, to provide us with an absolutely accurate internal clock. An internal clock that would dictate our biological rhythms irrespectively of how dark it is outside or at what time we set our alarm clock. The benefits would include no jet-lag, no need to reset the clock for summer and winter time and no need for watches to tell us what time it is. However, there would also be some really handicapping limitations. If our internal clocks could not be reset, it would be very difficult to travel over time zones, not to mention re-locating. A Texan moving to Australia would become an obligate nocturnal animal and vice-verse. Working nights would be even more painful that it already is as our ability to adapt to a reversed day-night cycle would be very limited. So, whoever created us wisely provided us with the capability to adjust our internal clock and circadian rhythms to our surrounding environment.

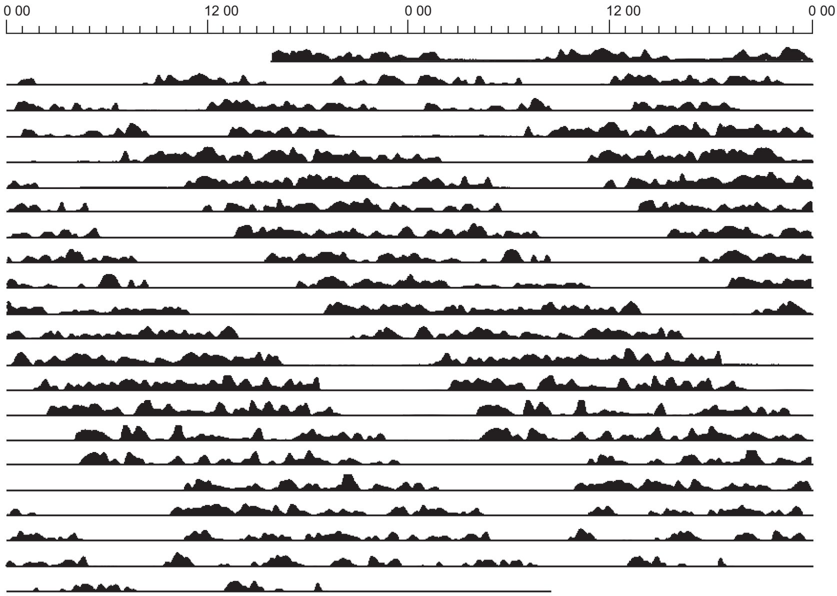
My interns during residency training, you know who you are, typically needed a nudge here and a cue there to function properly. They would gravitate towards the on call room (the sleepy type), the cafeteria (the hungry type) or the library (the overachieving type) if left to their own devices. Similarly, the internal clock constantly receives guiding cues from the outside environment. What would happen to our internal clocks if they were never set or never reset? And to be set and reset are in fact two different things. For ones internal clock never to have been set would require no exposure to light. Ever. For the internal clock not to be reset, several days' deprivation of light and other zeitgebers would be sufficient. Do we know what happens to our sense of time and biological rhythms in these scenarios? The answer is yes. But before we explorer further, let's consider the following figure.



The figure on the previous page illustrates. It is data from actigraphy, a watch-like device you wear on your wrist which records movement over several days. As we move much less when we sleep as compared to when we are awake, actigraphy data is a way of estimating sleep-wake patterns over a prolonged period of time. The black bars represent activity level, the higher they are the more activity. As you can see on the x-axis, each line represents a day of the week. On the y-axis you can see the time of day from 12 noon to 12 noon the following day. The central portion of this figure, where activity is mostly absent, represents sleep. Can you tell at what time this individual typically went to bed and at what time he or she woke up?

It looks like bedtime was 11 pm to midnight and wake up time was 7 to 8 am. As I am sure you realize, we don't know for a fact that this person actually slept from midnight to 7 am, we only know that there was no or little wrist movement during these hours. Nonetheless, it would be a pretty mind numbing task to lie completely still for 7 hours. Even when watching TV or reading a book we do move our arms every so often. So let us assume that, being aware of the limitations with this method, we trust the data.

Now, let's take a look at individuals whose internal clock was never set, individuals who where never exposed to light. Where could we find such a person? People living close to the North Pole only live in darkness for part of the year, and during that period they are exposed to artificial light. No ethics review board would approve a research study where you would deprive a person completely of light from birth. The answer, as you may have guessed, is that although nobody can be kept in the dark for an entire lifespan, some people are unable to register light. These are not legally blind individuals, who typically have some entrainment or setting of their internal clock by sunlight, but people with total blindness and no light perception. Having been born with total blindness guarantees that the internal clock was never set to natural or artificial light. Does this mean that a person with no light perceptions biological rhythms is completely uninfluenced by external factors? No,



as we have seen there are other zeitgebers. However, sunlight is by far the most powerful and biologically important one so having had no light exposure to entrain your internal clock is the closest we can get to an untouched, unaltered circadian rhythm.

So, what happens if we put an actigraphy device on an individual with no light perception in an environment void of other zeitgebers? Take a look at the figure above and try to interpret the data. Do note that you have a 48 hour cycle on the y-axis as opposed to 24 hours in the previous figure.

What happened? Well, clearly the blank spaces which represent sleep are not aligned top to bottom as in the previous example of a seeing individual. In fact each successive period of sleep seems to occur about 2 hours later than the preceding one. In other words, if this person started off sleeping from 11 pm to 6 am, the following night he or she would sleep from 1 am to 8 am, then 3 am to 10 am and so forth. Can you figure out in how many days the cycle perpetuates itself? It looks like it takes about 12 days.

This is what we call a free running cycle and more than half of all totally blind individuals exhibit this type of sleep-wake pattern. Is that bad? Does it have any negative health consequences? Not really, the only downside is that it might or might not be difficult to keep up with social functions if your sleep-wake cycle is not in synch with that of the rest of the world.

And there is a remedy that helps a totally blind person get synchronized with the seeing. We discussed previously how sunlight and darkness set the internal clock by inhibiting or promoting melatonin production in the brain. As it becomes darker outside, inhibition of melatonin production by light is decreased and more melatonin is produced. Melatonin signals that it is evening and time to prepare to sleep. How about just skipping the first step, decreasing light exposure to the eye, and give artificial melatonin? In fact, this treatment option is almost always successful. Melatonin is the treatment of choice for patients with no light perception and a free running sleep-wake cycle that desire treatment. Although melatonin is considered a mild drug when used as a sleep aid in seeing individuals, in this case, in setting the internal clock in the complete absence of light, it is very effective.

Although a free running sleep cycle is seen almost exclusively in the totally blind, it has been reported in the sighted as well. So if you think you are suffering from this condition, it is not impossible.

In this chapter we have familiarized ourselves with circadian rhythms and melatonin. We have talked about zeitgebers and sleep-wake patterns in individuals whose internal clock was never set but, as you may have noted, we omitted discussing what happens if the internal clock is not reset. That is, if you confine a sighted individual to complete darkness without any other zeitgebers. The reason for the omission was not that this experiment was not conducted. In fact it has been performed and repeated several times over, and the result suggested something so surprising, controversial and counter intuitive that it deserves a chapter of its own.

How long is a day on planet Earth?

Since the beginning of human life on our planet, many of the living conditions such as availability of fresh water, temperature and regional precipitation has changed dramatically from time to time. Not only from one geological area to another, but even between generations. But not everything has changed. One of the few things that have remained relatively constant has been the duration of a day. I say relatively constant because the duration of a day is actually increasing by 1.7 milliseconds per century. There are also fluctuations in the Earth's rotation rate which require the International Earth Rotation and Reference Systems Service to add or subtract a leap second when necessary to keep us on track. In case you missed it, the latest adjustment as of this writing was an addition of 1 second on December 31, 2008.

Now, this is all very fascinating, but what has it got to do with sleeping? Well, it gives us a perspective of the constancy of the day-night cycle our ancestors were exposed to, and it sets the stage for us when answering the main question of this chapter, which in full is: How long is a day on Earth according to our internal clocks?

It is one of those questions you never ask because the answer is so obvious. Like why do bodyguards wear bullet proof vests or what happened to Jimmy Hoffa? Knowing that we humans have been around on this planet for hundreds of thousands of years, the duration of a biological day and a solar day should be the same. Only a child or a crazy person would ask such a question. Jurgen Aschoff was neither, but he asked it anyway.

Born the youngest son of the famous pathologist Ludwig Aschoff, known to everyone in medicine as the fellow who discovered Aschoff bodies, the classical finding of rheumatic fever, Jurgen went on to study medicine at the University of Bonn. After graduating, he was recruited to the University of Gottingen to study temperature regulation in humans and discovered, by experimenting on himself, that his body temperature varied in a predictable and repetitive manner in a cycle over 24 hours. This finding sparked an interest that was to seal his destiny and secure him a position among the all stars of medicine. Jurgen devoted the rest of his career to the study of biological timing and is considered the father of this field, which we now call chronobiology. In particular, what propelled his rise to fame were a series of experiments over 20 years that are remembered to this day as the sleep bunker experiments.

In 1963, Jurgen and his colleagues, to investigate the function of our internal clock, begun admitting volunteers to a sound- and lightproof bunker from World War II. The subjects would stay in complete isolation from the outside world for 3-4 weeks with no exposure to zeitgebers. Food was placed in a refrigerator at random times and the subjects kept themselves busy reading or listening to a record player. Various physiological factors that were known to have a circadian rhythmicity such as body temperature and the calcium content of urine were recorded. The first subject to enter the bunker was Jurgen himself. He wanted to experience what living with no zeitgebers would be like.

Apparently, after having overcome the initial curiosity to know what time it was, he enjoyed living in a timeless environment. Over the following 20 or so years, over 300 people entered the bunker and the behavior of the subjects was consistent in one surprising aspect, their average day was no longer 24 hours.

The subjects in the sleep bunker lengthened their days to on average between 24.7 hours and 25.2 hours. The biological markers that were measured also adapted to these longer cycles. In a few extreme cases, subjects developed days that were more than 30 hours long. One such subject, a university student who had planned to study for an exam that was scheduled shortly after completing the experiment, refused to come out after 4 weeks. He had estimated studying 14 hours per day, when in fact it took him closer to 20 hours. So when the experiment ended, he thought he still had several days left to prepare for the exam.

I bet a lot of you reading this are thinking: Aha, that's why I'm always tired. I'm a 25 hour person trapped in a 24 hour day! And that's really what made these results so controversial. It seemed like all of us are prisoners in size S day, when in fact we are a size L, trying to bust ourselves out of confinement by staying up late, skimping on sleep and abusing coffee. Now before we discuss this further let's see if there was any criticism of the bunker experiments.

At the time of Jurgen Aschoff's famous investigations, it was thought that only the strong light of the sun (1000 lux on an overcast day and 25000 lux in full daylight) was capable of resetting the internal clock as opposed to the much weaker light (190 lux from a 100 watt light bulb at 10 feet) that artificially surrounds us. However, we know now that even weak light in the 100 to 200 lux range can cause disruptions in biological rhythms. To put things in perspective, 1 lux is approximately the amount of light produced by a single candle. Being aware of this, Dr. Charles Czeisler and his team at Harvard studied subjects exposed for 4 weeks to dim light, 15 to 20 lux, and forced them to live in an environment where bedtime was 4 hours delayed every day, effectively creating a 28 hour per day and 6 days per week environment. This so called forced desynchronization protocol was aimed at completely separating the rhythm of the internal clock from that of the surrounding environment. By establishing the timing of hormone secretions (cortisol, melatonin) and variations in body temperature, they concluded that the subject's circadian rhythm was maintained at 24.18 hours or 24 hours and 11 minutes. That is, despite being forced to live in a 28 hour day, the internal clock kept biological functions ticking in a 24 hour 11 minute cycle.

Between the experiments of Aschoff and Czeisler, several other studies have been conducted to shed light on the duration of a biological day. And although several support Aschoff's original findings, the currently prevailing opinion in the field of sleep physiology, is that the internal clock, without outside interference, is naturally running at a little over 24 hours.

If we for arguments sake agree with Czeisler that a biological day is 24 hours and 11 minutes rather than 25 hours, one might say that this really is not that different from 24 hours and 0 minutes. And from a perspective of sleep medicine, the difference is perhaps not that impressive. However, if we compare this biological day of 24 hours and 11 minutes with a solar day, which is 86400 seconds with just a few seconds of mean variation over centuries, the difference is monumental. Huge. But what does that difference mean? Does it mean that whatever created us was sloppy and imprecise? Or that despite hundreds of thousands of years on this planet, we still refuse to accept that a day only has 24 hours? Actually, these 11 minutes of discordance were provided to us for a specific purpose. Adaptability. The key to survival in an ever changing environment. This difference in a biological day and a solar day not only helped our ancestors stay competitive in an unpredictable world, but also gives us the temporal wiggle room we need to adapt to demands of a modern society such as crossing time zones and working in shifts.