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Abbreviations

Aβ	amyloid (plaques)
ADHD	attention deficit hyperactivity disorder
ADP	adenosine diphosphate
ANP	atrial natriuretic peptide
ASA	acetylsalicylic acid
ASD	autism spectrum disorder
ASPD	advanced sleep phase disorder
ATP	adenosine triphosphate
AVP	arginine vasopressin
BMI	body mass index
BPH	benign prostatic hyperplasia
BSB	Banking Standards Board
BST	British Summer Time
CBD	cannabidiol
CBTi	cognitive behavioural therapy for insomnia
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease caused by the SARS-CoV-2 virus
CPAP	continuous positive airway pressure
CSA	central sleep apnoea
DDAVP	desmopressin
DSD	driver safety device
DSPD	delayed sleep phase disorder
DST	Daylight Saving Time
EEG	electroencephalogram
EMA	European Medicines Agency
EMF	electromagnetic field
FDA	US Food and Drug Administration
FSH	follicle-stimulating hormone

GABA	gamma-aminobutyric acid
GMT	Greenwich Mean Time
GnRH	gonadotrophin-releasing hormone
HbA1c	glycated haemoglobin
hCG	human chorionic gonadotrophin
HDL	high-density lipoprotein
HRT	hormone replacement therapy
IVF	*in vitro* fertilization
LDL	low-density lipoprotein
LE	light emitting
LH	luteinizing hormone
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NDD	neurodevelopmental disorder
NREM	non-rapid eye movement sleep
nVNS	non-invasive vagal nerve stimulation
OCD	obsessive-compulsive disorder
OHS	obesity hypoventilation syndrome
OPN4	opsin gene encoding melanopsin
OSA	obstructive sleep apnoea
PD	Parkinson's disease
PKC	protein kinase C
PMDD	premenstrual dysphoric disorder
PMS	premenstrual syndrome
PPI	proton-pump inhibitor
pRGC	photosensitive retinal ganglion cell
PRR	pattern recognition receptor
PTSD	post-traumatic stress disorder
RBD	REM sleep behaviour disorder
REM	rapid eye movement sleep
RLS	restless-legs syndrome
SBD	sleep-related breathing disorder
SCN	suprachiasmatic nuclei
SCRD	sleep and circadian rhythm disruption

SDB	sleep-disordered breathing
SRED	sleep-related eating disorder
SRMD	sleep-related movement disorder
SSRI	selective serotonin reuptake inhibitor
SWS	slow-wave sleep
THC	tetrahydrocannabinol
TIA	transient ischemic attack
TNF	tumour necrosis factor
TST	total sleep time

Introduction

Nothing in life is to be feared, it is only to be understood.
Now is the time to understand more, so that we may fear less.

Marie Skłodowska-Curie

Forty years ago, as an undergraduate studying zoology at the University of Bristol, I knew I wanted to be a scientist, but I had little real idea of what that meant or involved. The 'body clock' was just a fuzzy concept in my young, unfocused free-wheeling brain. However, during the final year of my undergraduate degree, I was a volunteer helper at an international meeting on biological rhythms. The job was not demanding, and I swanned about listening to the lectures and met the then leaders of the field. With the confidence – perhaps arrogance – of youth, I assumed that these scientific titans would want to speak to me just as much as I wanted to speak to them. Most were incredibly generous with their time, although I did learn not to approach one very senior professor over breakfast (it's amazing how much meaning can be conveyed in a stony silence and a fixed stare at a greasy sausage . . .). It was a formative experience at many levels, and I soaked up the science like a sponge. Without my knowing it, this symposium defined my life-long interests and sparked an ambition to join this extraordinary group of international academics who were working on the fast-emerging science of biological time. My career as a scientist, from my undergraduate days to my current position as Professor of Circadian Neuroscience and Director of the Sir Jules Thorn Sleep and Circadian Neuroscience Institute at Oxford has allowed me to gain insights

from, and occasionally share new knowledge with, colleagues from all over the globe. In a sense, this book represents the distillate of what I have learnt in studying the nature of biological time over the course of four decades. My hope is that I can convey to you some of the excitement, wonder and undiluted pleasure I have experienced over the years.

In the past few decades, there has been an explosion of thrilling new discoveries in and around the science of the body clock and the 24-hour biological cycles that dominate our lives. The most obvious of these cycles is the daily pattern of sleep and wake. Surprisingly, most books discuss the body clock and sleep separately. However, new research tells us that such a disconnected approach tells only part of the story. You cannot properly understand sleep without understanding the body clock, and sleep in turn regulates the clock. In the pages that follow, the body clock and sleep will be considered together as two intimately linked and intertwined areas of biology that define and dominate our health. In so many cases, your ability to succeed or fail, from driving home safely after work or dieting to achieve weight loss, will depend upon whether you are working with or against these 24-hour cycles. So much has happened in this area of science and medicine that it is often difficult to disentangle fact from fiction. In terms of health, sensible advice is frequently transformed into strident orders that resemble the commands shouted by a Regimental Sergeant Major on the parade ground: you *'must'* get eight hours of sleep; you *'must'* continue to share a bed with a partner who snores; you *'must not'* use a light-emitting eReader (LE-eBook) before bed. So rather than being recognized as a loyal friend, biological rhythms and sleep are frequently portrayed as the enemy that needs to be wrestled, subdued and defeated. Instead, we need to understand and embrace these rhythms.

In this book, I have attempted to unpack the science of body clocks and sleep, making some of the amazing and exciting discoveries accessible, and hopefully in a format that is fun and easy

to read. I have been able to draw from my own personal experiences over the past forty years as a scientist in this field, and have benefited immensely from discussions with friends and colleagues, who have contributed directly to our current understanding of biological time. I provide the evidence behind our current knowledge of the science, and how this evidence can be used by each of us to make more informed decisions about improving our lives. From getting better sleep, to organizing our daily activities and even why we may benefit from taking medications or being vaccinated at a particular time of day. The information in this book will also give you a greater understanding of the behaviour of others, including why teenagers and the elderly might struggle to get restorative sleep, why your mood and decision-making skills may change from morning to afternoon, and why the risk of divorce is higher in those doing night shift work. I have emphasized throughout this book that we are all very different, and that while it *is* possible to make generalizations, taking an 'average value' can be misleading. Although the average length of the menstrual cycle in women is 28 days, only 15 per cent of women actually have a 28-day cycle. Your body clock and sleep biology can be likened to your shoe size: one size does not fit all, and making us all wear the same shoe size would be not only foolish but potentially harmful. The failure to recognize this variation is why some general advice in the media can be either overly simplistic or deeply unhelpful.

Sleep and daily rhythms emerge from our genetics, physiology, behaviour and the environment, and like most of our behaviours they are not fixed. These rhythms are modified by our actions, how we interact with the environment, and how we progress from birth to old age. From infancy to advanced adulthood, our body clock and sleep patterns change profoundly, but these age-related changes are not necessarily bad. We should stop worrying about our sleep and accept that 'different' is not necessarily worse. Some of the advice we are given can be just wrong, emerging

from the murky world of 'received wisdom'. Such 'wisdom' can be ancient and extend back to the beginnings of recorded history. However, as we shall see in the following chapters, the repetition of an idea does not necessarily guarantee legitimacy. For example, *flipping babies helps sort out their sleep*. According to this old tale, flipping the baby forward, head over heels, will reset the child's internal clock so that it will sleep at night and be awake during the day. There is absolutely no evidence for this. Indeed, as a tale it may well have its origins in parental desperation. Chronic sleep deprivation, not least in parents, can badly affect judgement and our ability to act rationally! Another often-repeated myth is that the pineal gland hormone melatonin is a 'sleep hormone'. It is not, and in the following chapters I shall explain why.

My message throughout this book is that all of us, as individuals and as members of society, should make some effort to understand and act upon the new scientific knowledge of biological time. But why bother? For me, it makes sense in a complex and demanding world to achieve the best physical and mental health we can. Such knowledge will help us deal with the many and varied insults that life flings at us. However, there is more. If you want to embrace life, be creative, make sensible decisions, enjoy the company of others, and view the world and all that it has to offer with a positive outlook, then embracing biological time will help you do this. Why not make the most of the time we have, and maybe even extend that time?

The Tick-Tock of the Biological Clock

The entrenched arrogance which goes with being human means that most of us assume that we are above the grubby world of biology, and that we can do what we want, at whatever time we choose. This assumption underpins the modern 24/7 society, and an economy that is dependent upon night shift workers to stock

our supermarkets, clean our offices, run our global financial services, protect us from crime, repair our rail and road infrastructure, and, of course, care for the sick and injured when they are most vulnerable. All of this happens while most of us sleep, or at least try to sleep. Although night shift work is the most obvious disruptor of our body clock and sleep, many of us experience shortened sleep as we try to squeeze more and more work and leisure activities into a daily schedule that is already over-packed and bursting at the seams. So we push these 'additional' activities into the night. Our full-scale occupation of the night has been possible because of the widespread commercialization of electric light across the world since the 1950s. This extraordinary and wonderful resource has also allowed us to declare war upon the night, and, without really appreciating what we have done, we have thrown away an essential part of our biology.

We are, of course, *not* able to do what we want at whatever time we choose. Our biology is governed by a 24-hour biological clock that advises us when it is the best time to sleep, eat, think, and undertake a myriad of other essential tasks. This daily internal adjustment allows us to function optimally in a dynamic world, 'fine-tuning' our biology to the profound demands imposed by the day/night cycle generated by the 24-hour rotation of the Earth upon its axis. For our bodies to function properly we need the correct materials in the right place, in the right amount, at the right time of day. Thousands of genes must be switched on and off in a specific order. Proteins, enzymes, fats, carbohydrates, hormones and other compounds have to be absorbed, broken down, metabolized and produced at a precise time for growth, reproduction, metabolism, movement, memory formation, defence and tissue repair. All this requires a biology and behaviour that are prepared and ready at the right time of day. Without this precise regulation by an internal clock, our entire biology would be in chaos.

For a relatively new branch of biology, and an emerging branch

of medicine, the science of body clocks has its roots much earlier than might be expected, going back to the late 1720s and the study of a plant with the Latin name of *Mimosa pudica* – meaning 'shy, bashful or shrinking' – also called the 'sensitive plant'. This member of the pea family, familiar to many gardeners, has delicate leaves which fold inward and droop when touched or shaken, and then reopen a few minutes later. In addition to responding to touch, the leaves fold up at night and open during the day. Jean-Jacques d'Ortous de Mairan, a French scientist, studied these plants.

De Mairan's seminal observation, for our story, was that *Mimosa* leaves continue to show this rhythmic folding and unfolding leaf movement for several days in complete darkness. He was amazed; it was clearly not the change in light and dark that was driving this cycle, so what could it be – could it be temperature? Daily changes in temperature were investigated in 1759 by another French scientist, Henri-Louis Duhamel du Monceau, who took *Mimosa* plants into a salt mine, where there were conditions of constant temperature and darkness, and found the rhythms continued. More than 100 years after this, in 1832, a Swiss scientist, Alphonse de Candolle, studied *Mimosa* plants under constant conditions and showed that these drifting or 'freerunning' rhythms in leaf opening and closing were not exactly 24 hours but around 22–23 hours.

Over the next 150 years, daily rhythms that continued under constant conditions with a rhythm close to, but not exactly, 24 hours were observed in many plants and animals. Such rhythms were later called *circadian rhythms* (*circa* means 'about', and *dia* 'a day'). However, it was fairly late in the game that circadian rhythms were studied in humans. Hints that they exist in us came from observations in the late 1930s by Nathaniel Kleitman. From 4 June to 6 July 1938, Kleitman and his student Bruce Richardson remained deep in Mammoth Cave, Kentucky. There was no natural light and the temperature was a constant and cool 12.2°C.

Light was provided by lanterns, so conditions were not completely constant. And they had to share the cave with a large population of curious rats and cockroaches. To stop them crawling into their bedding, the four legs of their bunkbed were placed into large tins containing disinfectant. They recorded sleep and wake times and measured their daily rhythm of body temperature. These observations showed that they continued to show roughly 24-hour cycles in body temperature and sleep/wake timing.

The true significance of these findings was not realized until the 1960s. One of the pioneers in the field, Jürgen Aschoff had an underground 'bunker' built in Andechs, a town in Bavaria with a Benedictine monastery that has brewed beer since 1455. University undergraduates, when not in the bierkeller, were housed underground in the bunker under constant dim light, and isolated from any external environmental time cues, but they did have access to a bedside lamp. So, again, they were not really under constant lighting conditions. Student sleep/wake cycles, body temperature, urine production and other 'outputs' were measured over many days and were shown to have a rhythmic daily pattern of about 24 hours under these semi-constant conditions. From such experiments, the human body clock was estimated to run at around 25 hours. More recent studies from Charles Czeisler's group at Harvard University suggest the average human clock ticks with a rhythm closer to 24 hours and 11 minutes. This difference in period was always a point of friction between Aschoff and the Harvard team. And the consensus today is that the difference was caused by the use of bedside lamps in the bunker experiments. Aschoff was a remarkable man and I learnt much from him – both scientifically and socially. About twenty-five years ago at a summer school party in Bavaria I opened a bottle of wine. Several minutes later there was a roar from Aschoff: 'Who has left the cork on the corkscrew?' I admitted that it was me and he said for all to hear: 'You *never* leave the

cork on a corkscrew, it is the height of bad manners.' I have never done it since.

By the 1960s, circadian rhythms, which persist (freerun) under constant conditions and have a period close to but not exactly 24 hours, had been identified in many different plants and animals, including us. And everyone (well, nearly everyone) accepted that these rhythms were generated biologically – they were 'endogenous'. As in all branches of science, unless you live under a dictatorship, there is never complete agreement about anything. But dissent is good because it makes scientists refine their experiments to build an even stronger 'evidence base' for the hypothesis being tested. The most prominent dissenter was Professor Frank Brown at Northwestern University in Chicago. He believed that biological rhythms were driven by some natural geophysical cycle such as electromagnetism, cosmic radiation or some other, as yet unknown, force. Brown's central, and not unreasonable, argument was that no biological mechanism could be independent of temperature. When you increase temperature, biological reactions speed up, while cooling slows them down. But for a clock to keep time accurately it has to always run at the same speed. More observations were needed, and studies in plants and 'cold-blooded' insects showed that biological clocks would indeed keep good time – despite huge changes in environmental temperature. Brown was wrong, but his challenge led to experiments which showed conclusively that biological clocks were indeed 'temperature compensated'. Endogenous 24-hour biological clocks had to exist!

An internal clock allows you to not only know the time, but also to predict time, or at least predict regular events within the environment. As I mentioned, our bodies need the correct materials in the right place, in the right amount, at the right time of day, and a clock can anticipate these different needs. By anticipating the approaching day our bodies are prepared in advance so that the 'new' environment can be exploited immediately. Blood

pressure and metabolic rate, along with many biological processes, rise before the new dawn. If we merely responded to the light of dawn to switch us from sleep into activity, then valuable time would be wasted getting our energy usage, senses, immune system, muscles and nervous system tuned up for action. It takes several hours to switch from sleep to activity, and a poorly adapted biology would be a major disadvantage in the battle for survival.

Two of the three essential features for an internal circadian clock have been touched upon so far – the ability to keep ticking with a period of about 24 hours under constant conditions, and to maintain a near 24-hour period even when environmental temperatures vary dramatically, showing temperature compensation. The third feature is called 'entrainment'; this capability is incredibly important and will be discussed in detail in chapter 3. I am, perhaps, a little biased about the importance of entrainment because this is what I have worked on for most of my career. As mentioned, circadian clocks do not run at exactly 24 hours, but tick a little faster or a little slower. In this way, circadian rhythms resemble an old mechanical grandfather clock which needs a slight daily adjustment to make sure the clock is set to the 'real' astronomical day. Without this daily resetting, the clock will soon drift and be out of alignment (freerun) with the environmental day/night cycle. A biological clock is of no use unless it is set to local time. For most plants and animals, including us, the most important 'entrainment' signal that aligns the internal day to the external world is light, especially the changes in light around sunrise and sunset. In us, and other mammals, the eye detects dawn and dusk to entrain our circadian rhythms, and eye loss prevents this resetting. People who have lost their eyes as a result of genetic disease or in combat, or because of a tragic accident, drift through time, experiencing periods when they get up and go to bed for a few days at the correct time, before they drift off again and want to sleep, eat and be active at the wrong time of day. A body clock with a period of 24 hours 15 minutes would take around 96 days

to travel from 12 noon back around to 12 noon again, getting later by 15 minutes each day. Blind individuals experience something similar to constant jet lag. They become 'time blind', a state that I will discuss in detail in later chapters.

The Big Sleep

Although the sleep/wake cycle is the most obvious of our 24-hour rhythms, hardly anybody talked about sleep at the meetings I attended in the early days. Sleep seemed to me, and to so many others at the time, too murky and nebulous a subject to get clear answers about. Sleep was also associated with abstract philosophical notions such as the 'mind', 'consciousness' and 'dreams'. It was too impenetrable for most of us. This notable lack of interest in sleep by most circadian researchers, including myself back then, reflected the divergent origins of the fields of circadian and sleep research. The science of circadian rhythms was established by biologists working on every sort of plant and animal. By contrast, sleep research has its origins in medicine and recordings of the electrical activity from the human brain – 'brainwaves'. Sleep was, and still is, studied intensively using electroencephalography (EEG), and interests were focused on how the EEG changed during different stages of sleep and disease. Based upon the size and speed of brainwave activity recorded from the brain by EEG, as well as eye movements and muscle activity, sleep is defined as either rapid eye movement (REM) sleep, or one of three stages of non-rapid eye movement (NREM) sleep. When we are awake our EEG shows small and rapid oscillations in our brain's electrical activity, but as we descend into NREM sleep these oscillations become larger and slower until we reach our deepest sleep, often called slow-wave sleep (SWS). From this state of deep sleep, the EEG transitions into faster and smaller oscillations once again and we enter REM sleep, which has been called

'paradoxical sleep' because it resembles the EEG seen during wake. During REM sleep we also experience paralysis from the neck down, while our eyes move rapidly under our eyelids from side to side – hence the name. This NREM/REM cycle occurs every 70–90 minutes, and across a night of sleep we experience four or five NREM/REM cycles, waking naturally from REM sleep. Around 15 years after the experiment in Mammoth Cave, Nathaniel Kleitman and another student, Eugene Aserinsky, discovered and named REM sleep in 1953 and linked REM to the time when we experience our most vivid and complex dreams. If you have a dog, you may have noticed that while asleep the dog may whimper or growl and make running movements as if chasing a rabbit. Such behaviours have led some to suggest that dogs, and indeed many mammals, also experience dreams during REM sleep. If you don't have a dog, you can always watch your sleeping partner in REM. It's fascinating, but a bit disconcerting for them if they wake and become conscious of your scrutiny!

It is only in the past 20 years, and most notably during the last 10, that circadian and sleep researchers have begun to talk to each other seriously and attend the same meetings. Indeed, meetings nowadays are designed to attract both groups of scientists, and today I consider myself to be both a circadian *and* a sleep researcher. So what got me into sleep? In my case there was a clear and defining moment, arising from a short discussion that irritated me intensely. In my former job, I spent quite a bit of time in the same building with neurologists and psychiatrists, and back in 2001 I bumped into a psychiatrist in one of the unreliable lifts at Charing Cross Hospital in west London. 'You work on sleep, don't you,' he said to me. 'No,' I replied politely, 'I study circadian rhythms.' He continued, oblivious of this subtlety, and said, 'My patients with schizophrenia have terrible sleep, and in my view that's because they don't have a job – so they go to bed late and get up late, which means they miss my clinic, are socially isolated and so can't make friends.' This 'unemployment' explanation

made no real sense to me, so I teamed up with another psychiatrist to study patterns of sleep in a group of 20 individuals with a diagnosis of schizophrenia. We compared sleep in this group to unemployed individuals of the same age. The results left me gobsmacked. Sleep/wake patterns in people with schizophrenia were not just bad, they were smashed, and utterly different from the unemployed individuals, who showed similar sleep patterns to employed individuals.

Individuals with schizophrenia also had very little or no SWS and abnormal REM sleep. I wanted to know why sleep had fallen apart in these individuals, and this provided the starting point to study sleep in mental illness, and then later in other health conditions. Interestingly, many of my circadian colleagues, for a whole variety of different reasons, have also 'moved into sleep' in the past decade. Perhaps age has given us wisdom, or maybe courage? Even more importantly, a new generation of neuroscientists armed with multiple and powerful techniques to examine the brain have chosen to study sleep, and are now delivering amazing new information.

Although a host of fundamental questions remain, sleep today is no longer regarded as the 'black box' that it was when I started research. Remarkable new work has greatly improved our fundamental understanding of how sleep is generated within the brain, and how sleep is regulated by our environment. We also now appreciate that during sleep we establish most of our memories, solve problems and process our emotions; we remove dangerous toxins that build up during activity; we rebuild metabolic pathways and re-equilibrate energy reserves. And if we fail to get sufficient sleep, brain function, emotions and physical health all fall apart rapidly. For example, abnormal sleep makes us more vulnerable to heart disease, Type 2 diabetes, infections and even cancer. In short, our sleep defines our ability to function while we are awake, and lack of sleep and the circadian disruption of sleep impact enormously on our overall wellbeing and health. While

the evidence demonstrating the importance of sleep is clear, this massive chunk of our biology, around 36 per cent of our life, is still not fully appreciated by many sectors of society. In five years of training, most medical students will have only one or two lectures on the topic, and the information covered is usually about EEG activity during sleep, rather than the new science of circadian rhythms and sleep that I will discuss in this book. In the public domain there remains a lot of sloppy thinking about sleep. Employers assume that their night shift workers will adapt to the demands of working at night. This assumption is wrong, and as a result employees can become dangerously ill, overweight and mentally impaired, and are at a higher risk of divorce and road accidents. As our society becomes increasingly 24/7, and as we squeeze more and more into an overcrowded day, our sleep has become the hapless victim.

What I Hope to Achieve

My central aim is to empower you, the reader, by providing concrete information and guidance, based upon the latest science. You will be able to use the information in the following chapters to get a better understanding of what makes your body clock 'tick' and, critically, use this knowledge to develop an optimal personal routine that works for you, irrespective of age or circumstances. I want to cut through some of the myths, and maybe burst a few bubbles, including the view that teenagers are lazy and that the business executive who gets up at 4 a.m. and starts work is a role model. As you will see, this book encompasses a huge span of human biology and will hopefully stimulate you to dig deeper into many of the topics covered.

Each chapter will consider a central topic, define the science of that topic, and then address issues that impact upon our health and wellbeing. Some of the science can get a bit complex, but it is

fundamental for gaining an understanding of our biology and health. The book is also structured so that you can jump back easily to earlier chapters and re-check information for a reminder. Finally, each chapter will finish with a short 'Questions and Answers' section designed to answer some questions that people frequently put to me and my colleagues. This Q&A section will also provide additional and sometimes oblique information. I stress that it is not my intention to provide medical advice; you should always seek this from your medical practitioner. But I will try to explain how some of your actions may be important in achieving optimal health and avoiding potential harm. Such actions include: why to eat at a particular time, when to exercise or when to take different medications, and why you should not drive in the early hours of the morning. This will not be 'finger wagging'. The aim is to provide you with the most up-to-date information that you can either adopt or ignore, but with a clear understanding of the consequences of your actions.

You will also find an Appendix I which provides some guidance on how you may want to develop your own sleep diary to monitor your sleep/wake patterns. Appendix I also includes a questionnaire which will allow you to estimate your 'chronotype', and whether you are a 'morning', 'neutral' or 'evening' person. Appendix II provides a brief outline of the immune system, digging a bit deeper into the complexity of this important part of our biology, which is covered in chapter 11. And in terms of detail, this book has been fully referenced, and I have been guided by one of my scientific heroes, Thomas Henry Huxley, who said: 'If a little knowledge is dangerous, where is the man who has so much as to be out of danger?' To help you build upon the 'little knowledge' in this book, I have cited the relevant scientific papers that have informed the discussion. Many of these scientific publications are, or will be soon, available online as a result of 'Open Access', whereby published research can be accessed free of cost. Indeed,

most scientific papers are freely accessible from scientific journal websites 12 months after publication.

My hope is that you enjoy this book and become inspired by the emerging science of biological rhythms, and, importantly, that you will want to apply this science to your own health, happiness and wellbeing. I also hope that, after a suitable period of reflection, you will agree with me that by embracing this knowledge you will be more creative, make better decisions, gain more from the company of others, and view the world and all that it has to offer with a greater sense of curiosity and wonder.

Oxford, January 2022

1.

The Day Within

What is a body clock?

I know who I was when I got up this morning, but I think
I must have been changed several times since then.

Lewis Carroll

Syncopation is a musical term meaning a variety of different rhythms played together to make a piece of music. By analogy, our biology is syncopated and we are the product. Everything about us is rhythmic. The electrical impulses generated in our nervous system, the beating of our heart, the release of hormones from glands, the contractions of the muscles regulating our digestion, along with a myriad of other processes, are all driven by rhythmic, endogenous changes in our bodies. And some of these rhythms relate to where we live.

One of the oldest intellectual challenges, faced by all civilizations, has been to discover the nature of our home. Our solar system established its current distribution of planets orbiting around the Sun around 4.6 billion years ago, and like other planets the Earth formed as a result of gravity pulling swirling gas and dust into a distinct solar body, making the Earth the third planet that orbits around the Sun. The early Earth was molten due to frequent collisions with other masses; indeed, the proto-Earth is thought to have sustained a massive impact with a Mars-sized body named 'Theia'. The Moon probably formed from the 'ejecta' from this collision about 100 million years after the formation of the

solar system. This impact is thought to have knocked the Earth off its 'daily' rotational axis so that the Earth now tilts about 23.4° away from its orbital axis around the Sun, although there is a slight 'wobble' of a few degrees. This 23.4° tilt, as we orbit around the Sun, causes our yearly cycle of the seasons. During part of the year, the northern hemisphere is tilted towards the Sun (summer) and the southern hemisphere is tilted away (winter). Six months later, the situation is reversed. Critically, the Moon's gravitational pull stabilizes the Earth's axial tilt, moderating the degree of wobble. This has produced a relatively stable climate on Earth for billions of years, and many believe that life on Earth would never have got started without this stabilization by the Moon. Paraphrasing the song by the Rolling Stones, we are *all* children of the Moon.

The bottom line is that today we sit on a relatively stable and rhythmic planet that is around 4.5 billion years old with a daily rotational axis of 24 hours, or 23 hours, 56 minutes and 4 seconds to be precise. Around 600 million years ago, when complex life was emerging, a day lasted only 21 hours, so the Earth is slowing down. But that's another story. Our Earth currently orbits around the Sun every 365.26 days, and the tilt of the Earth on its rotational axis generates the seasons. The Moon orbits around the Earth approximately every 29.53 days and its gravitational interaction with the Earth and Sun produces the tides. Collectively, these geophysical movements generate the day, night, seasons and tides. Many animals, indeed most life forms, have evolved body clocks of various kinds that anticipate at least one, and sometimes all, of these environmental cycles: daily, annual and lunar.

Rhythmicity is such a ubiquitous feature of life and our everyday experiences that we take it for granted. Perhaps this detachment is unsurprising. Most of the time we cannot sense our internal workings, and in the industrialized nations, at least, the natural day/night cycle is overridden by electric light and artificial heat. The Sun never really sets for *most* of us, and the seasons no longer

dictate our diet or where we live. Food is constantly available. In the UK we can buy strawberries from Kenya or southern California all year round, but as recently as 25 years ago the home-grown strawberry season was only six weeks long. Warmth at home or at work is accessed by the flick of a switch. We are now insulated from the environmental cycles that dominated our evolution. A major aim of this book is to reacquaint us with one of these cycles – the 24-hour cycle of day and night.

The study of physiology aims to understand how living things work. It's a huge discipline that includes the molecular processes within cells, how the nervous system works, the regulation of hormones, how the various organs of the body function and the generation of behaviour in all its varied forms. Human physiology, like that of most other animals, is organized around a 24-hour cycle of activity and rest. In the active phase, when food and water are sought and then consumed, organs need to be prepared for the intake, processing, uptake and storage of nutrients. The activity of organs such as the stomach, liver, small intestine and pancreas, and the blood supply to these organs, needs to be appropriately adjusted across the day and night. During sleep, we stay alive by mobilizing our stored energy. This energy is then used to drive many essential activities including the repair of body tissues, the removal of harmful toxins, and the formation of memory and the generation of new ideas in the brain. Because physiology shows such a marked daily pattern, it should be no surprise that our performance, the severity of disease, and the action of prescription drugs change across the 24-hour day. A few examples of these rhythmic 24-hour circadian changes are shown in Figure 1. Such rhythms have been observed for centuries, and, of course, the long-asked question has been 'Where do they come from?'

For hundreds of years, one of the main goals in understanding the brain has been to identify what parts of the brain do what, and it is truly a daunting task. You will read in many textbooks that there are 100 billion neurones in the human brain. Nobody

Melatonin
Melatonin, ng/mL-1
25.0
12.5
0
Cortisol
Cortisol, ng/mL-1
15
7.5
0
2 p.m.
10 p.m.
6 p.m.
2 a.m.
10 a.m.
6 a.m.
Clock time
Growth hormone
Plasma growth hormone, µg/L
20
10
5
Testosterone
Testosterone, ng/ml
8
6
4
Temperature
Core body temperature, °C
37.5
37.0
36.5
36.0
Multiplication accuracy
Relative score
200
150
100

Figure 1.

Figure 1. Examples of 24-hour daily changes in human physiology. Shown here are representations of the daily changes seen in physiology: the hormone melatonin from the pineal gland (Figure 2)[1]; growth hormone released from the pituitary gland[2]; body temperature[1, 3]; the 'stress hormone' cortisol from the adrenal glands[1]; testosterone produced by the gonads (the testes in men and by the ovaries in women) and in small quantities from the adrenal glands[4]; and multiplication accuracy, representing one aspect of our cognitive abilities[3, 5]. Many hormones, such as cortisol, are released as 'pulses', and so shown here is the 'smoothed average' of hormone release. There are two important points to make about these rhythms. First, these are averages, and there will be differences between individuals relating to when these rhythms peak and their size or amplitude. The second point is that many of these rhythms were not recorded under constant conditions, and while they almost certainly have a circadian component, meaning they would persist for many cycles under constant conditions, they are more accurately called 'diurnal' changes. The significance of these changes will be discussed in later chapters.

seems to know quite where this figure came from, but anyhow it is wrong. The Brazilian researcher Suzana Herculano-Houzel undertook some careful studies to finally address this question, and her answer was that the average human brain contains around 86 billion neurones.[6] Now, I know this might sound a bit like the medieval debate on 'How many angels can dance on the head of a pin?', but a difference of 14 billion neurones is a lot of neurones. There are about 14 billion neurones in the *entire* baboon brain, and, for additional comparison, 75 million in the mouse brain, 250 million in the cat, and 257 billion in the elephant. So 86 billion is a lot of neurones, which is why the discovery that only 50,000 work together as a 'master biological clock',[7] coordinating our 24-hour circadian rhythms, is a truly remarkable achievement.

This 'master clock' in humans, and all mammals, is located in an area of the brain called the 'suprachiasmatic nuclei', or SCN (Figure 2). The discovery of this structure has a fascinating history. Researchers in the 1920s had noted that rats under constant conditions of darkness run in a running wheel (similar to the hamster wheels you can buy in a pet shop) with rest (sleep)/activity rhythms that are a little shorter than 24 hours. This observation was a bit of a shock because the prevailing view in the 1920s was

that behaviour occurs as the result of a particular stimulus – a bit like a reflex. You provide a specific stimulus, and you get a specific kind of response. However, the rats showed a rhythmic pattern of daily activity without any obvious external stimulus. The activity pattern appeared to be generated from within the animal, and not driven by changes in light or other stimuli. So what was driving this rhythm?

Experiments in the 1950s and 1960s on rats removed different organs of the body to try to identify this 24-hour driver, but near 24-hour rest/activity rhythms persisted under constant conditions. The rat's brain was then examined. Small parts of the brain were surgically removed (lesioned), and rest/activity patterns examined. If you think it was bad for rats, remember that at this time lobotomy was a routine operation in humans, a procedure whereby most of the connections to and from the prefrontal cortex (Figure 2, p. 24) were cut in an attempt to 'cure' psychiatric conditions, and the chap that invented this technique got a Nobel Prize. The experiments on rats suggested that 'the clock' must reside somewhere deep in the brain, probably the hypothalamus (Figure 2), because destruction of this tiny area of the brain resulted in 'arrhythmicity', or the complete loss of any 24-hour patterns of activity and rest.[8] These studies were then followed up in the early 1970s, and the SCN (suprachiasmatic nuclei) emerged as the prime candidate.[9, 10] Almost 20 years later, the final and critical role of the SCN was confirmed in golden hamsters. In the late 1980s, Martin Ralph and Michael Menaker, who were close colleagues of mine at the University of Virginia, discovered a 'mutant' hamster, the '*Tau* mutant hamster', with an activity/rest pattern of 20 hours, compared to the non-mutant animals which had a pattern close to 24 hours. The SCN of a *Tau* mutant hamster (20 hours) was transplanted into the hypothalamus of a non-mutant hamster (24 hours) whose own SCN had been lesioned and showed complete arrhythmicity. Remarkably, the mutant SCN not only restored circadian rhythms in wheel-running behaviour, but,

critically, the restored rhythms were 20 hours – not 24! Transplanting other parts of the hamster brain had no effect. These findings showed that the transplanted SCN must contain 'the clock'.[11] I remember these experiments vividly, and the incredible excitement we all felt as the data were collected on a daily basis and we observed that the restored rhythms were 20 and not 24 hours.

As mentioned, the SCN contains about 50,000 neurones,[7] and a remarkable finding was that each has its own clock. This was again first shown in rats, where the rat SCN was separated out into its individual cells and placed into cell culture. The electrical activity of individual SCN cells was then monitored and showed robust and independent circadian rhythms – all ticking away at a slightly different time to each other. What's more, these individual SCN neurones kept on ticking in a dish for weeks.[12] As SCN cells were shown to have a clock, the clock mechanism had to be located within the cell – there had to be a molecular clock! This was remarkable stuff indeed, and demanded an answer to the question: how is this rhythm generated?

In 2017, three researchers from the USA, Jeffrey C. Hall, Michael Rosbash and Michael W. Young, shared the Nobel Prize for discovering how the clock 'ticked'. They did this after almost 40 years of research, sometimes working together and at other times as rivals, with many young scientists all contributing a little piece of the jigsaw. I was working at the University of Virginia while some of the key discoveries were being made, and Hall, Rosbash or Young would visit and give a seminar about the latest progress. As scientists, they were equally brilliant, but as characters they were completely different, each with a very 'distinctive personality'. For example, Jeff Hall is also a notable scholar of the American Civil War, and on one memorable occasion visited the University of Virginia and gave a research seminar about his latest progress on the molecular clock dressed in a Northern Unionist Army tunic and cap. This choice of attire, which was possibly designed to provoke, was completely ignored by the Faculty in the heart of

Figure 2.

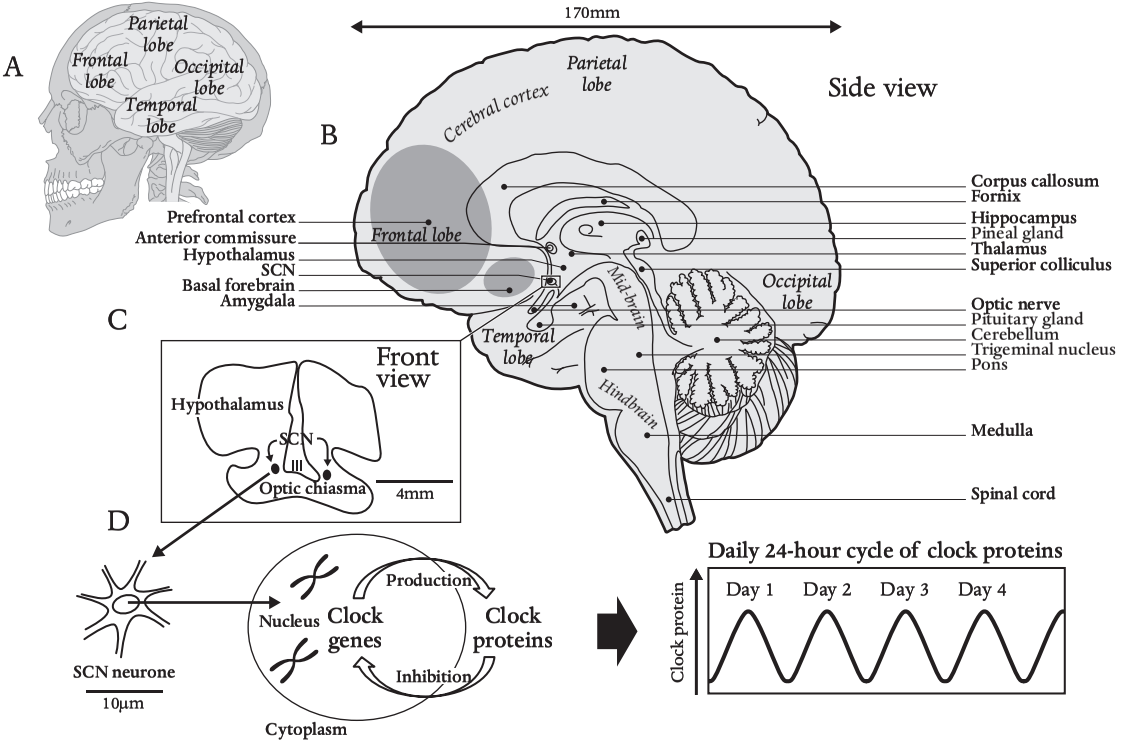
A
Parietal lobe
Frontal lobe
Occipital lobe
Temporal lobe
170mm
B
Side view
Cerebral cortex
Parietal lobe
Frontal lobe
Occipital lobe
Temporal lobe
Mid-brain
Hindbrain
Prefrontal cortex
Anterior commissure
Hypothalamus
SCN
Basal forebrain
Amygdala
Corpus callosum
Fornix
Hippocampus
Pineal gland
Thalamus
Superior colliculus
Optic nerve
Pituitary gland
Cerebellum
Trigeminal nucleus
Pons
Medulla
Spinal cord
C
Front view
Hypothalamus
SCN
III
Optic chiasma
4mm
D
SCN neurone
10µm
Nucleus
Clock genes
Production
Inhibition
Clock proteins
Cytoplasm
Daily 24-hour cycle of clock proteins
Clock protein
Day 1
Day 2
Day 3
Day 4

Figure 2. **A.** Shows the location of the human brain within the skull and the most obvious brain lobes (parietal, frontal, occipital, temporal) that can be recognized from the outside of the brain. **B.** Provides a view of the brain along a mid-section from the side, and indicates the location of the key internal structures. The typical human brain comprises about 2 per cent of the body's total weight, but uses 20 per cent of our total energy intake. As little as five minutes without oxygen can cause brain cells to die, leading to severe brain damage. The brain is 73 per cent water, but it takes only 2 per cent dehydration for brain function such as attention, memory and other cognitive skills to be badly impaired. Our brains have usually finished developing by the age of 25. **C.** Shows an enlargement of the suprachiasmatic nuclei (abbreviated to SCN) from the front. The SCN represent the 'master biological clock'. The SCN sit either side of the third ventricle of the brain (III) and above the optic chiasma, which is where the optic nerves enter the brain and fuse. A small number of nerves within the optic nerve, called the retinohypothalamic tract, enter the SCN and provide light/dark information from the eye for entrainment (chapter 3). **D.** Shows a single SCN neurone, which is around 10μm (0.01mm) in diameter. The SCN has around 50,000 neurones and each can generate a circadian rhythm. Normally they are all connected to each other. Clock genes are located in the nucleus of each SCN neurone and create a message that guides the building of clock proteins. These proteins are made in the cytoplasm that surrounds the nucleus. The clock proteins then interact to form a protein complex which moves into the nucleus to inhibit or 'switch off' the production of further clock proteins. After a while, this protein complex is then broken down (degraded), which allows the clock genes to make clock protein once again. A roughly 24-hour cycle of protein production and protein breakdown is the result. This molecular feedback loop is converted into a signal (electrical or hormonal) that acts to coordinate the circadian clocks in the rest of the body.

the 'Old South'. Science is often portrayed as a linear march from ignorance to enlightenment. It is nothing of the sort; there are always mistakes and dead ends, and it is fascinating to recollect how often these extraordinary scientists got it wrong, and sometimes badly. But, as the facts accumulated, the lessons were learnt, the hypothesis was adjusted, the mistakes were quietly forgotten and progress once more resumed. That's science.

The progress being made by Hall, Rosbash and Young was not on humans or even mice, but on a very distant animal relative, the tiny fruit fly called *Drosophila*, the very same fly that swarms around the fruit bowl in summer and is often squashed without a second thought. *Drosophila* remains one of the most commonly

used 'model species' to understand how genes give rise to physiology and behaviour, and has been studied for more than 100 years.[13] These flies are relatively cheap to care for, they breed rapidly and have exquisitely well-understood genetics, all of which has made them indispensable for basic research, including research into the circadian clock. So what did Hall, Rosbash and Young discover in *Drosophila*? At its core, the pathways in the cell that generate the 'molecular clockwork' consist of a 'negative-feedback loop', which consists of the following steps (Figure 2D): clock genes located in the nucleus of the cell create a message that provides the template to build clock proteins. These proteins are made in the cytoplasm (the matrix part of the cell that surrounds the nucleus). The clock proteins then interact to form a protein complex which moves into the nucleus to inhibit or 'switch off' the production of further clock proteins. After a while, this protein complex is then broken down, which allows the clock genes to do their stuff once more and make more clock proteins. A 24-hour cycle of protein production and protein breakdown is the result. And this is the molecular clock, well . . . more or less! The rates of clock gene activation, protein production, protein complex assembly, protein complex entry into the nucleus, inhibition of clock genes, protein complex breakdown and then reactivation of the clock genes all combine to produce a 24-hour rhythm, and changes (genetic mutations) in any one of these steps can either speed up, slow down or break the clock.[14] It was just such a mutation in the '*Tau* mutant hamster' that gave it a period of 20 rather than 24 hours.[15] The molecular clockwork of all animals, including you and me, is built in a very similar way. This is all the more remarkable when you think we shared a common ancestor with *Drosophila* more than 570 million years ago, when the Earth had a 22- to 23-hour day, suggesting that our biological clocks have had to slow down by a few hours over the past hundreds of millions of years.

The 24-hour rhythm of clock protein production and

degradation acts as a signal to switch on and off countless genes and the circadian production of their proteins that, in turn, regulate rhythmic physiology and behaviour (Figure 1). Our current understanding of the 'molecular clockwork' is the most complete example in any field of biology of how genes ultimately give rise to behaviour, and, for this first molecular characterization of a circadian rhythm in *Drosophila*, Hall, Rosbash and Young richly deserved the trip to Stockholm and their Nobel Prize, the presentation of which I was lucky enough to witness.

Interestingly, small changes in our clock genes (polymorphisms) have been linked to whether we are a 'morning', 'evening' or 'intermediate' body clock type. Morning types, or 'larks', like to sleep early and get up early, and it seems that they have faster body clocks, due to changes in one or more of their clock genes.[16] By contrast, evening types, or 'owls', have slower clocks and prefer to go to bed later and sleep in. So, by their contribution to our genes, our parents are still telling us when to get up and go to bed! Our body clock type is often referred to as our 'chronotype', and, as we shall discuss later, our chronotype is also influenced by our age and when we are exposed to light around dawn and dusk. You can explore your own chronotype with the information in Appendix I.

Although the SCN is the 'master clock' in mammals, it is not the only clock.[17] We now know that there are clocks within the cells of the liver, muscles, pancreas, adipose tissue, and probably in every organ and tissue of the body.[18] Remarkably, these 'cellular peripheral clocks' seem to use the same negative-feedback molecular clockwork as the SCN clock cells. This came as a big shock. I remember when Ueli Schibler, working at the University of Geneva, first presented his findings at a meeting in Florida in 1998 showing that non-SCN cells had clocks.[19] There was an audible gasp from the audience. Clock genes had previously been identified in non-SCN cells, but for many years these genes were thought to be doing something else, and the idea that cells outside the SCN could contain clocks was not seriously considered. The

reason for this was that destruction of the SCN abolished the 24-hour rhythms of activity and hormone release of the sort illustrated in Figure 1. The conclusion from SCN lesion studies was that the SCN 'drives' 24-hour rhythms throughout the body. But we now appreciate that this idea was an oversimplification. Loss of observable rhythms after SCN lesions is due to two key factors: the first is that many individual peripheral clock cells 'dampen out' and lose their rhythmicity after several cycles – they run out of steam without a gentle nudge from the SCN. The second and more important cause is that without a signal from the SCN, individual clock cells in tissues and organs become uncoupled from each other. The cells continue to tick individually, but at slightly different times, so that a coordinated 24-hour rhythm throughout the entire tissue or organ is lost.[20] It's rather like visiting a stately home where all the antique clocks start to chime at slightly different times. This discovery led to the appreciation that the SCN acts as a pacemaker to coordinate, but not drive, the circadian activity of billions of individual circadian clocks throughout the tissues and organs of the body. The SCN is rather like the conductor of an orchestra: it provides a time signal that coordinates the rest of the orchestra/body, and without the conductor/SCN everything drifts apart, so instead of a symphony you have a biological cacophony, and a failure to do the right thing at the right time.

The signalling pathways used by the SCN to synchronize, or entrain, these 'peripheral clocks' are still uncertain, but we know that the SCN does not send out countless unique signals around the body that target different tissues and organs. Rather there seems to be a limited number of signals which include the autonomic nervous system (that part of the nervous system responsible for control of the bodily functions not consciously directed) and several chemical signals. The SCN also receives feedback signals from other parts of the body, including the sleep/wake cycle, that adjust its activity, allowing the whole body

to function in synchrony with the changing demands of the 24-hour day.[20–21] The result is a complex circadian network that coordinates rhythmic physiology and behaviour. The loss of synchronous activity between different circadian clocks, either within an organ or between organs such as the stomach and liver, is called 'internal desynchrony' and can cause serious health problems, which I will discuss in later chapters.

The circadian system fine-tunes our bodies to the varied demands of the 24-hour day/night cycle. But unless this internal timing system is set to the external world it is of no practical use, and it is this alignment of the 'internal' and 'external' day that I want to consider in chapter 3. But before that I want to take a look at sleep, that most obvious of our 24-hour patterns of behaviour, in the next chapter.

Questions and Answers

1. How many clock genes are needed to build a molecular clock? Long gone are the days when we talked about 'the' clock gene. It is difficult to put an exact number on this as it depends on what you mean by a clock gene. A workable definition would be that clock genes are like the cogwheels of a mechanical clock. They interact in a specific way to generate a 24-hour rhythm, and if you take one of these 'cogs' away, or damage a cog, the clock will be significantly altered or even stopped. Using this definition, there are around 20 different clock genes in us and other mammals like mice that drive the molecular clockwork.[22] However, this is a bit misleading as there are very many more genes that contribute to the regulation of the clock, the stability of the clock, and then how the clock drives circadian physiology. If we include these genes there may be hundreds. Also, it is worth being aware that all of these 'clock' genes have other roles, regulating biological key processes such as cell division and the regulation of metabolic processes.

2. Are human circadian rhythms influenced by electromagnetic fields (EMFs)?
Currently there is no strong evidence that EMFs can alter human circadian rhythms.[23] But absence of evidence is not evidence of absence. I think it fair to say that if there is an effect it is small.

3. Do humans have annual clocks?
We do show a variety of annual rhythms, including peaks in birth, hormone release, suicide, cancer and death. For example, in the northern hemisphere, and perhaps counterintuitively, suicide in spring is significantly higher than in the winter around December, when suicide rates are at their lowest.[24] Some argue that we are like sheep, deer and many other mammals that have an annual clock. But this is difficult to demonstrate experimentally as volunteers would need to be housed under conditions of constant light and temperature for at least three years; and the ethics of such experiments, let alone the practicality of finding volunteers, are unacceptable. Others argue that we do not have an annual clock, like a circadian clock, but are merely responding directly to annual changes in the environment such as day length or temperature.[25]

4. Do all animals have a suprachiasmatic nuclei (SCN)?
All mammals, including the marsupials (e.g. kangaroos) and egg-laying monotremes (e.g. duck-billed platypus), do have a structure in the brain that resembles an SCN. When experiments have been undertaken, the SCN seems to act as the 'master' clock, coordinating the circadian rhythms of the peripheral clocks. But this is not the case in birds, reptiles, amphibians and fish. In these animals there are several organs that can act as a 'master clock'. These are located in SCN-like structures within the hypothalamus, the pineal organ and even the eyes. A big puzzle is that in closely related species the importance of and interaction between the SCN, pineal organ and eyes vary considerably. For example, in the house sparrow, the pineal organ seems to be the dominant clock, while

in the quail the eyes play this role. In pigeons, all three organs interact![26] This topic fascinated one of the pioneers of circadian research, Michael Menaker, who became a close friend and colleague when I was based at the University of Virginia.

5. Do the genes and proteins of the molecular clockwork regulate non-clock behaviours too?
Yes – and, as discussed in chapter 10, mutations in clock genes have been linked to cancer, and other conditions such as mental illness (chapter 9). Remarkably, an increased desire to consume alcohol has also been linked to changes in some of the 'clock genes'.[27] When a single gene is involved in more than one activity this is called a 'pleiotropic gene'. And this is the rule rather than the exception.

6. Have humans evolved weekly or monthly biological rhythms?
This has been much debated. While it is clear that life on Earth has evolved clocks to predict geophysical cycles such as the 24-hour rotation of the Earth, the seasons and the Moon-driven tides, evidence for internal clocks that predict man-made cycles such as the week or month is far less clear. Some have argued strongly in favour,[28] but most circadian biologists argue against the existence of biological clocks with a 7- or 31-day period on the basis that there is no robust evidence.

2.

A Heritage from Our Cave Days

What is sleep, and why do we need it?

There is no scientific study more vital to us than the study of our own brain. Our entire view of the universe depends on it.

Francis Crick

In Greek mythology, Hypnos is the god of sleep. He is the son of Nyx (Night) and Erebus (Darkness), and his twin brother is Thanatos (Death). Hypnos and Thanatos live in the underworld (Hades). So even from ancient times sleep has been linked to darkness, death and hell. By association, sleep was hardly given a ringing endorsement by the ancients. And if we jump forward over 2,000 years to the twentieth century things don't get much better. The great entrepreneur Thomas Edison is reported to have said: 'Sleep is a criminal waste of time and a heritage from our cave days.' These may not have been his exact words, but Edison certainly would have agreed with another American, Edgar Allan Poe, who is supposed to have said: 'Sleep, those little slices of death – how I loathe them.'

Sleep, from the earliest times, has not been embraced. Indeed, during more recent centuries it came to be despised, partly because hard work was considered intrinsically virtuous and worthy of reward. Sleep stops us from working and so, by definition, sleep must be sinful. Of course, not all agreed with this view, and as you might expect, Oscar Wilde adopted a somewhat different attitude, explaining: 'Life is a nightmare that prevents one from sleeping.'

Sadly, the views relating to sleep held by Edison, Poe and many

other like-minded individuals were adopted by decision makers throughout the nineteenth and twentieth centuries. Although attitudes have improved more recently, sleep today is still regarded as a type of 'sickness' in need of a cure. Something we have to tolerate, but would rather not. And without all the facts we have waged war on this essential part of our biology. Such an ill-conceived action has resulted in appalling consequences for our individual health and wellbeing, along with a major economic insult for the state.

Within our brain, the generation of the daily sleep/wake cycle involves a highly complex set of interactions between the hind-brain, mid-brain, hypothalamus, thalamus, cerebral cortex (Figure 2, p. 24), and all the brain neurotransmitter systems (e.g. histamine, dopamine, noradrenaline, serotonin, acetylcholine, glutamate, orexin, GABA (gamma-aminobutyric acid)) and a few hormones, none of which are unique to the generation of sleep. These systems combine to broadly flip the sleep/wake states, rather like a seesaw, to either sleep or consciousness. But sleep is not an 'off' state, but rather a condition of intricacy and change.

The REM and NREM Sleep Cycle

For centuries, it was presumed that during sleep the brain was shut down and nothing much happened. Part of the reason for this assumption was that there were no real tools available to look at the sleeping brain until the 1950s. Since the 1950s sleep has been studied routinely in the laboratory by placing electrodes onto the skin of the scalp, stuck there by using an electrically conducting jelly, and measuring the pattern of electrical activity, called the electroencephalogram (EEG). I mentioned this in the introduction, but just to remind you: when awake, and during the early stages of sleep, the EEG pattern is fast (high frequency) and small (low amplitude). Think of the pattern you get when you rapidly