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The Circadian Clock and Human Health

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Epidemiological studies provided the first evidence suggesting a connection between the circadian clock and human health. Mutant mice convincingly demonstrate the principle that dysregulation of the circadian system leads to a multitude of pathologies. Chrono-medicine is one of the most important upcoming themes in the field of circadian biology. Although treatments counteracting circadian dysregulation are already being applied (e.g., prescribing strong and regular zeitgebers), we need to comprehend entrainment throughout the body's entire circadian network before understanding the mechanisms that tie circadian dysregulation to pathology. Here, we attempt to provide a systematic approach to understanding the connection between the circadian clock and health. This taxonomy of (mis)alignments on one hand exposes how little we know about entrainment within any organism and which 'eigen-zeitgeber' signals are used for entrainment by the different cells and tissues. On the other hand, it provides focus for experimental approaches and tools that will logically map out how circadian systems contribute to disease as well as how we can treat and prevent them.

Introduction

The circadian clock is a temporal programme found in organisms from all phyla. It is an adaptation to earth's rotation, conferring a 24-h structure on processes at all levels — from gene expression to behaviour. Circadian clocks are autonomous, producing circa-24-h rhythms even in the absence of daily environmental signals (zeitgebers). The mammalian circadian programme shows both top-down and bottom-up organisation. The ability to generate daily rhythms is a cellular quality. These cellular clocks form networks that build up the circadian programme in tissues, organs, and the entire organism. The top-down organisation in mammals is rooted in a nucleus located above the optic chiasm (the suprachiasmatic nucleus, SCN). This pacemaker receives photic information via the retina, synchronises its own neuronal cellular clocks, and transduces the 'internal day' to a network of peripheral clocks (see Box 1 for glossary of circadian terms).

In nature, clocks normally synchronise to their 24-h world; i.e., they don't free-run. This *entrainment* process has been described in detail and is highly systematic: the *phase of entrainment* (e.g., the relationship between dawn and the daily core body temperature minimum) is not fixed but depends on the relative strengths of zeitgeber and circadian clock (compare Figures 1A, B, E and F). It also depends on the length of the internal day produced by the circadian system — the shorter the day, the earlier the entrained phase; the longer the day, the later the phase. Successful entrainment equalises internal and external day length in all of us, while entrained phase can be variable from individual to individual, and from condition to condition (Figure 1A–F). Although clocks can entrain to zeitgebers that are longer or shorter than their internal day (Figure 1C,D), leading to systematic differences in phase of entrainment, this is only possible within certain limits (*range of entrainment*). Again, these limits depend on the relative strengths of zeitgeber and clock. Outside of their range of entrainment, circadian clocks alternate between breaking away in an apparent free-run and being transiently caught by zeitgebers, a phenomenon called *relative coordination* (Figure 1G) [1].

Only entrainment-related selection pressures shaped the circadian programme through evolution. Without entrainment, the system loses its main advantage — faithfully predicting the regular changes of its environment. Incorrect circadian predictions are even less advantageous than none at all (Figure 1G). Thus, all organisms evolved to adopt a specific phase of entrainment. The same mechanism that adjusts the entrained phase to changing photo- and scoto-periods is used by organisms that migrate or are transported over long distances as they adjust to changes in sun time, analogous to how modern man copes with trans-meridian travel. Entrained phases (or *chronotypes*) can vary greatly among individuals, creating a distribution of chronotypes ranging from extreme 'larks' to extreme 'owls', with the majority of individuals falling between these extremes [2]. The distribution is largely derived from genetic polymorphisms in clock genes [3], development (age) [4,5] and environment [6]. The impact of development on chronotype is best seen in adolescents, who are characterised by a late chronotype. Light environment, or more specifically zeitgeber strength and structure (e.g., more light in the morning than in the evening; see also Figure 1), will also lead to differences in entrained phase, between or within individuals. The combination of living indoors and nighttime illumination substantially weakens the amplitude of the zeitgeber and makes most people become a later chronotype (Figure 1 B,F). In winter, chronotype is also later, probably due to a combination of later sunrise and lower light levels [7]. Thus, the variety of chronotypes reflects the plasticity that is built into and essential for the entrainment process.

Traditional descriptions of entrainment pertain to the timing of behaviour, which is mediated by the interaction of the light environment and the SCN clock. Entrainment of the entire organism, however, concerns peripheral (cell- and organ-based) oscillators as well. A proof of principle therein is found in the internal phase relationships in rodents. In light–dark cycles, peripheral organs adopt a characteristic phase relationship to the SCN [8,9]. When the daily rhythms of clock gene products are compared, those in the periphery lag those in the SCN by several hours [10,11]. When animals are held in constant darkness (e.g., without

Box 1. Glossary of circadian terms.

(Underlined terms refer to other items in this glossary).
Alignment/misalignment: if circadian rhythms in the different organ clocks are not only synchronised to 24 h but also adopt normal phase relationships to one another, they are aligned; if they are synchronised to 24 h but adopt unusual phase relationships to one another, they are misaligned. Traditionally, this applies to the relationship between the circadian programme of an individual on one hand and the timing of the physical (e.g., light and darkness) and the social (e.g., school and work times) environment on the other. Here we apply this concept also to the relationship between different components of the circadian programme amongst each other (e.g., the clock in the SCN and that in the liver).
Chronotype: the circadian clocks in different individuals entrain differently to the light–dark zeitgeber — earlier or later depending on characteristics of the clock such as amplitude, light input pathway, response characteristics, etc. The relationship between the internal day and the external day (e.g., between the minimum of the core body temperature and dawn) is called 'phase of entrainment' or chronotype as it is used here. The term 'chronotype' is also used to describe a psychological personality trait associated with preferred daily times for different activities (such as sleep, food-intake, or exercise).
Entrainment: the process whereby circadian clocks actively synchronise to cyclic environmental signals (zeitgeber; predominantly light and dark).
External day: the 24-h structure of our environment — day and night and all the consequences of sunlight and darkness (temperature changes, food availability, enemy presence, etc.).
Free-run: circadian clocks can produce self-sustained rhythms even in a constant environment (i.e., without zeitgeber signals). Under these conditions, their rhythms run free.
Internal day: the 24-h structure of an individual's circadian programme, integrating the internal time of the SCN and that of all the cellular and organ clocks.
Internal phase relationship: when the clocks in the brain and those in the organs or different organ clocks establish a given phase relationship amongst each other.
Internal time: external time is defined into 24 units (hours) between one midnight and the next. Analogously, internal time can be defined into 24 units from, e.g., one mid-sleep or one core-body-temperature (CBT) through to the next.
Jetlag: syndrome describing the state of the circadian clock (internal time) in relationship with external time after travelling (e.g., by plane) across time zones. The syndrome arises because internal and external time, as well as the different organ clocks, are out of synch for several days. As a rule of thumb, the circadian system takes a day for each hour time change to adapt to the new light–dark cycle at the destination but this can vary depending on individual clock characteristics, light (and other zeitgeber) exposure and direction of travel.
MCTQ: the **M**unich **C**hrono**T**ype **Q**uestionnaire. An instrument that uses sleep-times to assess individual phase of entrainment (chronotype; see www.theWeP.org).
Phase: any point within an oscillation.
Phase of entrainment/entrained phase: the relationship between the internal day and the external day (e.g., between the minimum of the core body temperature and dawn).
Phase relationship: clocks that entrain to one another or are entrained to a common third oscillator assume specific phase relationships to one another. For example, their rhythm's peaks and troughs may coincide, lead or lag each other, or oscillate in anti-phase.
Photoperiod: the length of daylight from dawn to dusk, changing systematically with season depending on geographical location.
Range of entrainment: clocks can entrain to non-24-h zeitgeber cycles but only within given limits. The human circadian clock, for example, cannot entrain to 22 h or 26 h cycles.
Relative coordination: when a rhythm is not entrained but still influenced by a zeitgeber cycle, then it can alternate between a free-run and (transient) synchronisation.
SCN: the suprachiasmatic nucleus, a neuronal centre of the circadian system located above the optic chiasm. It receives information about light and dark via the eyes, entrains to those signals and relays this information to other clocks throughout the body.
Scotoperiod: the length of darkness from dusk to dawn, changing systematically with season depending on geographical location.
Social jetlag (SJL). the difference in daily behaviour between workdays and work-free days. SJL is quantified by the difference between the midpoints of sleep on work- and free days in hours.
Zeitgeber: regular cyclic environmental signals, e.g., light:dark, regular feeding.
Zeitgeber strength: the amplitude between maximum and minimum of the zeitgeber. For example, between the amount of light we are exposed to during the day and the level of darkness at night.

zeitgeber strength or structure), internal phase relationships re-establish themselves [12,13]. Although, we know that 24-h cycles of glucocorticoid or temperature synchronise most cellular clocks *in vitro* [14–17], we know little about the mechanistic details of intra-organismal entrainment *in vivo*. That the liver (and to some extent the kidney) synchronises to signals derived from

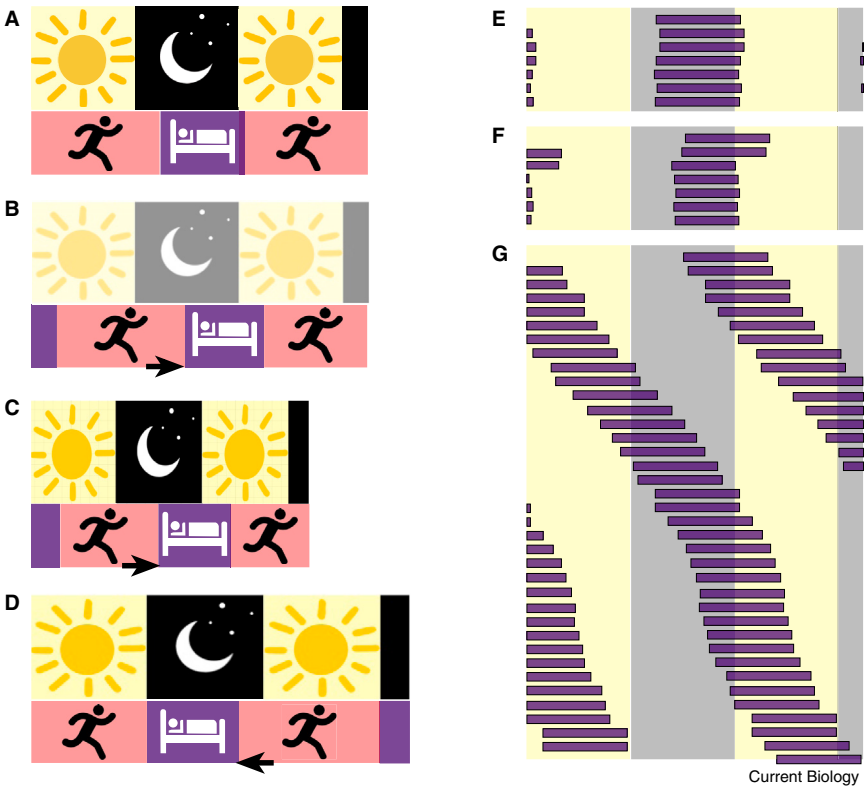

Figure 1. Entrainment of the circadian clock.
Different scenarios showing various relationships between zeitgeber cycles and circadian rhythms (here shown as light–dark cycles and sleep–wake behaviour, respectively). (A) Ancestoral/rural entrainment (strong zeitgeber; bright daylight and no artificial light at night): sleep onset falls well before midnight and sleep ends at around dawn. (B) Modern/industrial entrainment (weak zeitgeber; indoor light and artificial light at night): sleep onset at around midnight and sleep ends well after dawn (arrow: delayed phase of entrainment). (C,D) Within the limits of entrainment circadian clocks can entrain to zeitgeber cycles shorter or longer than 24 h, with delays in shorter and advances in longer cycles (arrows). (E) Double plot of the sleep times under ancestoral/rural entrainment conditions. (F) Double plot of the sleep times under modern/industrial entrainment conditions. The first two days represent a weekend when people can sleep according to their chronotype and the following five days represent workdays, where people have to get up early but cannot fall asleep early enough to prevent sleep deprivation. This scalloping sleep pattern has been coined social jetlag [33]. (G) When zeitgeber strength drops below a threshold, entrainment is lost but the zeitgeber cycle still modulates the free-run or through-run with relative coordination [1].

feeding [8,10,18,19] is well established, setting up potential conflicts between SCN as an endogenous zeitgeber and social factors (mealtime). Which 'map' of phase relationships between the SCN and the respective peripheral organs is optimal for health under different zeitgeber conditions is still open for discovery.

What Do We Know About the Circadian Clock and Human Disease?

The circadian clock was first implicated as a factor in various diseases through epidemiological studies showing increased incidences of cancers in long-term shift workers. A 1996 report suggested higher levels of breast cancer in Norwegian radio and telegraph operators [20]. Numerous follow-up studies using independent populations indicate that this is a robust finding, despite substantial variation between shift-work structures. Additional reports showed that colorectal and prostate cancers are also increased, as are metabolic and gastrointestinal disorders [21–23]. This has led the Danish government to compensate long-term shift workers with breast cancer [24] and the World Health Organisation to suggest a set of health risks linked with shift work [25]. The light-at-night (LAN) hypothesis placed the hormone melatonin at the centre of the cancer disease process. It argues that melatonin — beyond being a hormone — is a major scavenger of reactive oxygen species. Since melatonin is mainly produced at night and suppressed by light, the hypothesis claims that oncogenesis becomes more likely when people are exposed to light at night. The epidemiological evidence for the LAN–breast-cancer connection seems strong [26] and totally blind people are less likely to develop breast-cancer than sighted controls [27]. However, LAN is also the prime proxy for modern life-styles and consequently for circadian misalignment and social jetlag (SJL) [28], making the dissection of the causal network difficult. And the very assumption of how melatonin works has largely been revised, as it is recognised that it acts as a hormone binding to specific and clock-regulated receptors that have themselves been linked to disease phenotypes [29,30]. The fact that living against the circadian clock is associated with many melatonin-unrelated pathologies suggests additional aetiologies linking cancer and shift work. A circadian clock-centric hypothesis would focus on circadian misalignment — a sub-optimal form of entrainment — as a key factor in these pathologies. Recent experiments in mice that do not express melatonin and show exacerbated tumour formation in shift work experiments support this idea [31].

Shift work *per se* impacts approximately 20% of the workers in the western world, but a mild form of this condition may be far more widespread than these figures suggest: only 13% of the day-working population (represented in the MCTQ database) [32] do not suffer from SJL [32] (Figure 1F), a condition that resembles a mild but chronic form of shift work. SJL is defined as the difference in sleep timing between free days and workdays (expressed in hours) [33] and is the consequence of the alarm clock. Regular use of the alarm clock leads to both chronic sleep deprivation and to the performance of daily activities (eating, exercising, exposure to light) when one would normally be sleeping — at least during the workweek. In other words, alarm clocks lead to misalignment. Epidemiological studies show that SJL correlates with health problems: the odds of being overweight significantly increase with SJL (by 33% for every hour of SJL), as do disease-promoting behaviours such as addiction

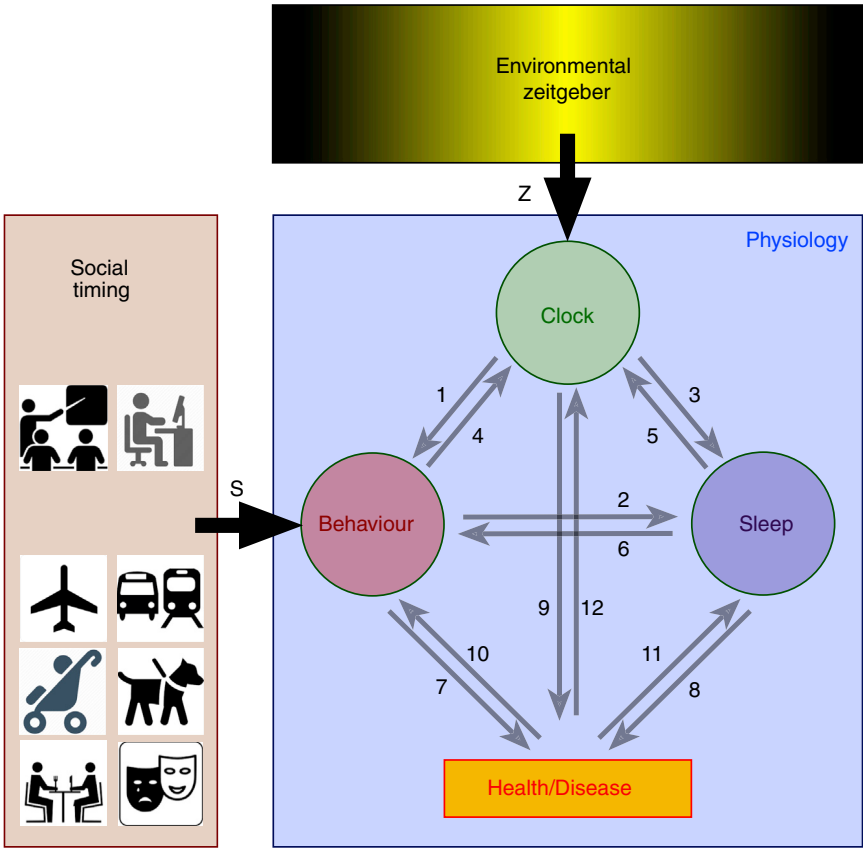

Figure 2. The circadian clock and disease.
Relationships and interactions between the circadian clock and disease may either be direct or indirect via behaviour and/or sleep (for description of arrow numbers see main text). Social schedules exert their influence on physiology mainly via behaviour (arrow S). The regular daily changes in the environment that the clock uses for its synchronisation (entrainment) to the 24-h world are indicated by arrow Z.

to nicotine and alcohol consumption [32,33]. Related to SJL is circadian misalignment resulting from daylight saving time (DST). The introduction of DST adds an hour of SJL in most people and it takes people weeks to adjust to the time change [7]. Increases in heart attacks have been observed after the DST change [34,35], similar to the increased risk for cardiovascular diseases reported for shift work and other circadian misalignment conditions [23,36–38].

Epidemiology can identify relatively small effects by investigating large groups and should therefore be useful in developing hypotheses concerning the causal network behind shift-worker-induced diseases. But the relationship between the circadian clock and human health involves a highly complex network of influences and confounders. For instance, health deficits can arise from both sleep deprivation and circadian misalignment [39] (Figure 2), which often occur simultaneously in shift workers.

Circadian misalignment and sleep deprivation often develop out of the timing of sleep — the only clock-related health condition classified by the ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10th edition). Code number G47.2 refers to 'Disorders of the sleep wake schedule' (as part of Chapter VI: Diseases of the nervous system), including 'Delayed sleep phase syndrome' and 'Irregular sleep-wake pattern'. Code number F51.2 (as part of Chapter V: Mental and behavioural disorders) refers to an overlapping set of disorders except that they derive from non-organic (psychogenic) causes. An improvement on the ICD-10 list is found in a Clinical Practice Guideline from the American Academy of Sleep Medicine (AASM) [40], which also specifies Advanced Sleep Wake Phase Disorder and Non-24-Hour Sleep-Wake Disorder. How to apply these becomes problematic as is apparent from the diagnostic guidelines, which refer to Advanced or Delayed Sleep Phase as two or more hours earlier or later, respectively, relative to desired or socially customary sleep times. Approximately 25% of the population satisfies this criterion according to the distribution of chronotypes [32] (derived from the MCTQ database as of November 2015, Roenneberg, unpublished). If the diagnostic guidelines were used rigorously, then we would be looking at an epidemic. This would furthermore be a modern epidemic, as the broad chronotype distribution is largely due to weak zeitgebers of modern life [6].

Why is the inability to sleep at an optimal social time — as constrained by the circadian clock — deemed a disorder, a disease or a health problem? When people have to sleep at suboptimal times they often feel exhausted and lethargic (sleep deprivation), sometimes also experiencing aches and pains as though they were getting a flu (possibly due to a state of internal jet-lag/desynchrony) and/or they show cognitive deficits (either due to the circadian changes in performance or to sleep deprivation [41]). Treatments recommended by the expert panel in the AASM guideline include light therapy or, more often, timed melatonin administration. In all cases, the evidence-base for these treatments is weak [40]. In no case is the rich distribution of chronotypes, representing young and old clocks with different amplitudes and periods in rural and urban or summer and winter light environments, considered in treatment recommendations.

Negative consequences arising from sleep timing are at least partially due to a discrepancy between the circadian sleep window and the social sleep opportunity. This discrepancy can be elicited when 'normal' chronotypes are forced to work at extreme times (e.g., night shifts) or when extreme chronotypes have to comply with 'normal' work hours. As indicated above, extreme chronotypes can derive from genetic disposition [3], age [4,5], zeitgeber conditions [6], or from a combination therein. The impact of the light environment on human chronotype has been investigated by a study [42] documenting activity/rest cycles and melatonin onset in urban life compared to outdoor camping (no artificial light at night and bright, natural light during

the days). The results clearly showed, firstly, that the variance in human chronotypes is enlarged by the weak zeitgebers characteristic of modern lifestyles and, secondly, that late (urban) chronotypes become significantly earlier when exposed to strong (natural) zeitgebers. Under extremely weak zeitgeber conditions, individuals can even run free (Figure 1G) or become apparently arrhythmic in their sleep–wake behaviour [43]. Total blindness (lack of all light reception) represents the most extreme version of this condition and, in these cases, failure to entrain is often observed [44] (Figure 2 and Table S1). Pathologies of the SCN (e.g., tumours [45]) disrupt the circadian clock's light signalling pathway and can lead to apparent arrhythmia.

Patients with neurodegenerative disorders such as Parkinson's, Alzheimer's and Huntington's diseases, or the more general classification of dementia, also show lack of consolidated sleep. Some of this may be due to disease-associated pathology [46,47], but there are also indications that low amplitude light–dark cycles contribute to this condition [48]. Indeed, when brighter lights were installed in an experimental paradigm, several measures improved from consolidation of sleep to mood and even the expected cognitive decline slowed. Children with Smith–Magenis syndrome have been studied for their poor sleep, and some show a concomitant abnormality in their melatonin profile [49], suggesting a problem with the central clock mechanism. Treatment with a combination of beta-blockers to suppress daytime melatonin and supplementation of nighttime melatonin is an effective therapy for these patients.

Seasonal Affective Disorder (SAD, sometimes also called winter depression) has been linked to the circadian clock [50]. This subset of major depression has a characteristic seasonal onset, and the circadian clock is involved in seasonal photoperiodic time measurement. SAD is therefore treated — beyond the treatments used for other types of depression — with light therapy, supplementing light exposure during the short photoperiods [51].

We have described two general strategies that have been used to establish disorders or diseases associated with the circadian clock. Epidemiology looks for associations based on many individuals. Several of these initial findings (especially concerning cancer and metabolic diseases) have been validated with evidence from highly controlled experimental approaches. [31,52,53]. This general approach indicates that small insults from chronic circadian misalignment lead to diverse pathologies. An alternative approach is based on using the clock itself to describe disease. The timing of sleep is used as a proxy of the circadian clock in the brain (the pacemaker) and misalignment or abnormal entrainment is considered the disorder. Both approaches underscore the importance of knowledge concerning the principle of circadian entrainment at every level of circadian organisation in order to understand the aetiology of misalignment-associated diseases and to develop strategies for treatment. We have to understand the principles of circadian entrainment throughout the entire body.

Circadian Health and Disease — a Matter of Entrainment

Here, we propose that the relationship between the circadian clock and health can only be understood by unravelling entrainment characteristics and mechanisms at all levels of the circadian network, i.e., not only how the SCN synchronises to the environment but also how all tissues and organs perform as part of an orchestrated, daily programme. The rules of entrainment apply to all of these levels, so that distinct entrained phases are expected also at the tissue/organ level. What do these phase maps look like and what phase relationships are tolerated?

The zeitgeber choices for the SCN are simple — it uses light to entrain. Coupling among SCN neurons contributes to this entrainment, leading to fine-tuning of amplitude and waveform [54]. There is evidence that the timing, shape and amplitude of the electrical activity in the SCN directly translate to the timing and the amount of locomotor activity [55]. Non-SCN cell and tissue clocks are bathed in neural and humoral endogenous zeitgebers [56], which act as 'eigen-zeitgebers'. Some cell-clocks in a tissue can couple with clocks in neighbouring cells, as in the SCN (although this is not a universal principle [57]). We know little concerning how these various factors and levels interact or what happens if they are inconsistent with one another.

As a starting point to describe the constellations of possible entrained phases (phase maps), we define *optimal entrainment* when SCN, other brain areas, kidney, heart, lung etc. adopt their characteristic internal phase relationships. Because we entrain differently at different times of our lives, at different times of the year and amongst each other, whether we live in cities or in the country, many phase constellations may represent *optimal entrainment*. This 'phase map' was shaped by evolution to allow all aspects of the body to cope optimally with the 24-h environment and it will be characteristic for different zeitgeber conditions and chronotypes. Deleterious phase constellations (circadian disruption [58], *social jetlag* [32], or circadian *misalignment* [53]) may develop under weak, conflicting or disrupted zeitgebers (both external and eigen-zeitgebers), resulting in decreased fitness or disease.

Neither the phase map for optimal nor that for sub-optimal entrainment has been formally defined in humans, but rodent experiments support their existence: the liver can entrain to feeding cycles [10,18], overriding SCN signals [59]. Further, by regulating the timing of eating, the effects of a high-fat diet on mice can be mitigated [60]. Depending on the experimental protocol, the clock genes in the SCN and the liver can oscillate up to 180° out of phase, demonstrating the tremendous plasticity of internal phase relationships. Can we define range limits and durations as to when this divergence becomes bad for health?

A proof of principle showing that the human phase map also depends on conditions comes from temporal isolation experiments (an environment with no time information). Humans often produce internal days of approximately 25 h in these conditions [61]. The internal temporal programme dictates the daily structure even to the point when the subjects expose themselves to light or darkness (e.g., by turning off the lights and closing their eyes for sleep). When we live under external zeitgebers the circadian core body temperature minimum (CBT_{min}) occurs sometime after the mid-point of sleep, but when humans live in temporal isolation CBT_{min} occurs at around sleep onset. Thus, a change of external conditions (albeit highly artificial) can change phase relationships of important functions such as sleep and temperature control by as much as four hours.

Experimental evidence further supports the hypothesis that internal phase maps are associated with health and disease.

A protocol called *forced desynchrony* dictates sleep–wake times (and therefore also light–dark exposure) in cycles that are outside of the range of entrainment (e.g., 20 or 28 h) [62]. Under these conditions, the CBT rhythm continues with its circadian period (≈ 24 h), while behaviour, locomotor activity and feeding are forced to follow a 20- or 28-h rhythm. The different body clocks experience the conflict of either following the forced sleep–wake cycle or the SCN, which runs through the forced cycle. An indication of how important phase maps are in dissecting clock-related pathologies comes from comparing central and peripheral rhythms under these conditions (e.g., by measuring melatonin/CBT, metabolites, cortisol, ions, performance, etc.). Without knowing the exact organ-specific phase map, we do know that they create a disease-like state. Metabolism in these otherwise healthy subjects is diagnosed as pre-diabetic after less than 10 days [52,53]. Similarly, in controlled experiments, chronic nocturnal sleep restriction leads to weight gain and lowered resting metabolism [63,64]. Interestingly, moving sleep–wake times to abnormal times is similar to what a shift-worker experiences regularly, and metabolic diseases are prominent among the illnesses of long-term shift workers (for review, see [23,65]). Results of experiments simulating shift work in mice also indicate that frequent zeitgeber shifts lead to weight gain [31], and *CLOCK* gene mutant mice are obese and have metabolic disease [66]. Thus, both a chronically strained clock (due to, for example, shift work) and a genetically 'broken' clock can lead to similar pathologies.

Formal Interactions Between the Clock, Sleep and Health

By definition, physiology represents organismal function at all levels. The circadian clock therefore is both a part of physiology and, as well, modulates it over the course of the day (Figure 2). This concerns gene expression [67], metabolism [68–70], immune [71–74] and endocrine [75,76] function as well as behaviour (arrow 1 in Figure 2) [77]. The timing of sleep depends on how long we were awake (process S; homeostasis; driven mostly by behaviour; arrow 2) but is also under strong circadian control (process C; arrow 3) [78,79]. The behavioural influences on sleep include the consumption of caffeine [80], alcohol and nicotine [33]. Behaviour also influences the clock (arrow 4) in the form of light sampling (via the SCN) and feeding (via the liver [19]). The influence of sleep on the circadian clock (arrow 5) has increased in industrialised societies since sleeping is often the only time when we expose our SCN to real darkness [6]. The effects of sleep on behaviour (arrow 6) are most obvious with sleep deprivation and performance [41,81].

The triangle clock–sleep–behaviour is instrumental in balancing health and disease. Social schedules (e.g., work and school times) predominantly act on the circadian/sleep network via behaviour (arrow S) and can lead to discrepancies between social and biological timing (SJL) [33]. These discrepancies may include being awake, sleeping and eating outside the times specified by optimal entrainment without substantially changing the clock's phase (similar to masking [82]). People working standard rotational shifts, for example, frequently revert to their usual free-day sleep times when they need not work [83], suggesting that the phase of the clock (as represented by the SCN) remains relatively stable (depending on roster and light exposure during the night shift). Despite this, as suggested above, unusual mealtimes adopted by shift workers should lead to suboptimal phase maps. Discrepant signals from the circadian clock and behaviour to physiology (e.g., to metabolism; arrows 7 and 9), predict metabolic syndromes [32,53,70,84,85]. Metabolic disorders also result from sleep deprivation (arrow 8) [86,87], which can derive from a consequence of a mismatch between behaviour and the clock (arrows 2 and 3).

Finally, the balance between health and disease clearly influences all of the three physiological subdomains — behaviour, sleep, and the clock. The most obvious influence of a pathology on clock function are blind people with a total lack of light reception [88]. Many of them do not entrain, showing patterns similar to that shown in Figure 1G because they cannot integrate light–dark zeitgebers (dysfunction of arrow Z), and the daily influences of behaviour (e.g., alternations between activity and rest, regular meal times; commonly called 'social zeitgeber'; via Arrow S) are too weak to entrain their circadian clock [44,89–93]. Some people are visually blind but (unconsciously) are light sensitive via photoreceptive ganglion cells. This class of blind people can entrain their clock [94]. Bedridden patients, who obviously experience both weak light–dark and rest–activity cycles (arrows Z and 4, respectively), should be susceptible to sub-optimal entrainment. Indeed, studies of critically ill patients in intensive care units found that circadian rhythmicity was often absent in many of the recorded vital parameters [95], a condition that may derive from zeitgeber, pathology or both. Some psychiatric diseases are associated with abnormalities in social behaviour and therefore in light-sampling behaviour. This would obviously also lead to unusual phases of entrainment, as have been reported [96]. Interestingly, various psychopharmaca have been shown to regulate the timing of sleep–wake behaviour: haloperidol can disrupt it while clozapine can improve consolidation [97].

The effects shown in the diagram of Figure 2 can be highly complex. Socially influenced behaviour (arrows S and 2) together with a late chronotype (arrow 3) can lead to altered sleep patterns (times and duration as well as the resulting dark exposures), which in turn can feed into the clock (arrow 5) and thus drive a positive feedback (arrows 1 to 2 to 5 to 1 etc.). If the external zeitgeber is weak (arrow Z), this could lead to *non-24-hour sleep–wake disorder*, the inability to entrain to the 24-h world despite apparently normal photoreception (Figure 1G) [91,98].

A Taxonomy of Circadian Misalignment

We have outlined the importance of circadian entrainment for health and proposed that misalignments between the different clocks in the circadian programme are potentially detrimental for health. Here, we describe a taxonomy of circadian phase maps (relationships between the SCN and peripheral circadian clocks). Figure 3A shows the elements of this taxonomy — four basic states of circadian systems represented by distinct icons:

- Green icons (state 1) represent optimal entrainment.
- Blue icons (state 2) refer to rhythms that are entrained with abnormal phase relationships to their respective zeitgebers — light for the SCN, food for the liver clock, and rhythmic endogenous signals (eigen-zeitgebers) for all peripheral clocks (note that the blue icons stand for delayed or advanced entrained phases). Reasons for abnormal phases are manifold [43]. Zeitgeber strength, timing or amplitude or

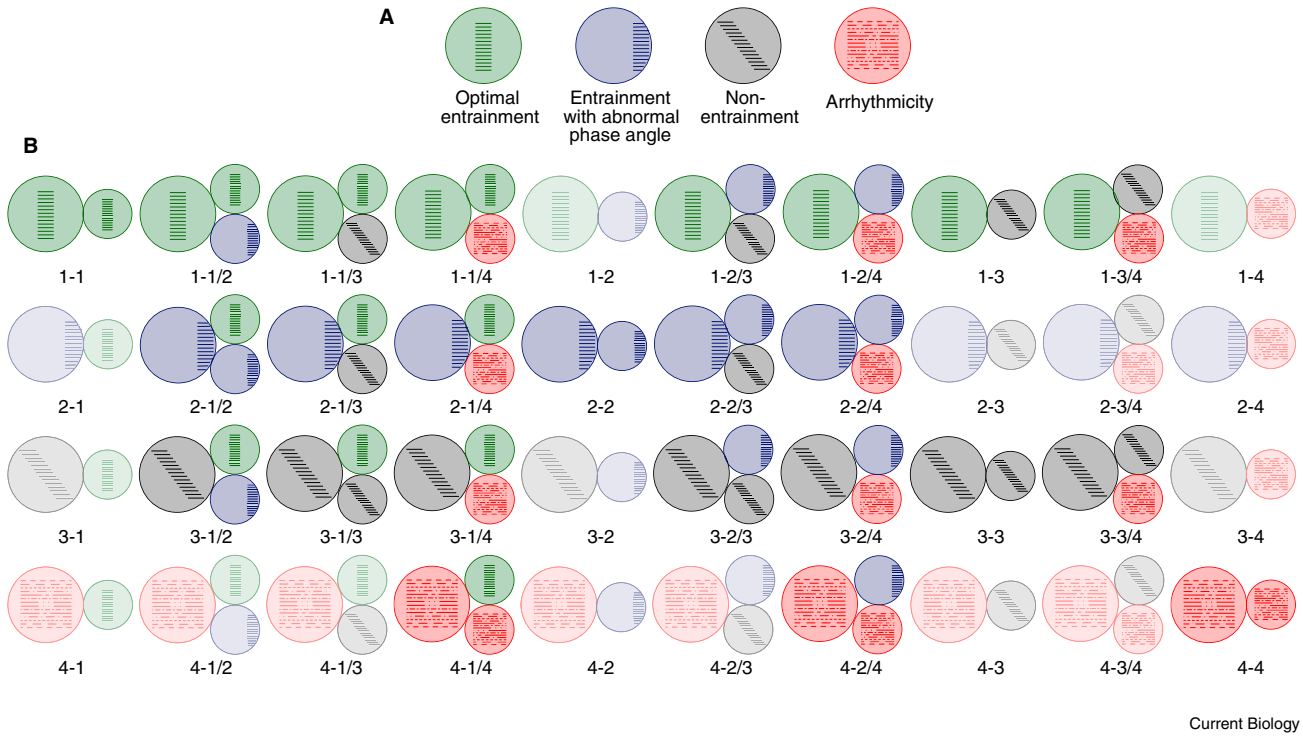

Figure 3. Entrainment between different components of the circadian programme.
(A) Representation of possible states of the circadian system. From left to right: the green icon (state 1) evokes the normal entrained state found in 'optimal entrainment'. The blue icon (state 2) represents a clock that entrains extremely late or early. The black icon (state 3) suggests failure to stably entrain despite a cyclic environment. The red icon (state 4) indicates arhythmicity. The icons (and the corresponding states) represent phenotypes and not necessarily genotypes (even wild genotypes that are normally rhythmic may be rendered arhythmic by zeitgeber strength or structure, e.g. constant light). (B) Different components of the circadian system may assume different states, depending on their distinct zeitgeber or eigen-zeitgeber environment. The numbers under the respective combinations refer to the states shown in panel A. The larger icons on the left of each combination represent the central SCN and the smaller icons on the right represent the tissues and organs in the 'periphery'. If all peripheral clocks have a consistent relationship, only one icon is shown, if tissues/organs resume different states, they are represented by two different icons. Constellations that are highly unlikely are more transparent. See also Table S1.

the sensitivity or transduction mechanisms of the circadian input pathways will impact entrained phase. Mutations that change the internal day length would alter the phase of entrainment. Since the principles of entrainment are the same for all oscillators, these mechanisms hold for both the entrainment by external zeitgebers (as in the case of the SCN by light or the liver by food) as well as the entrainment of peripheral clocks by endogenous eigen-zeitgebers.

- Black icons (state 3) represent rhythms that fail to stably entrain to zeitgebers or eigen-zeitgebers (free-run, through-run, relative coordination as in Figure 1G). This could happen for a number of reasons, for example if a zeitgeber has a period beyond the clock's range of entrainment or if it is too weak to entrain a robust circadian clock. Note that extremely short or long photoperiods may also represent weak zeitgebers. This icon refers to all sustained non-24-hour periods (either >24 or <24) lasting for at least several days, including the transitions during re-entrainment that occur with jetlag. Note that our day-to-day period also often deviates slightly from 24 h but in a non-sustained manner, where the average period over many days is exactly 24 h.
- Red icons (state 4) show an arrhythmic system which can arise for several reasons, for example due to a clock gene mutation (genetic arrhythmicity) as shown in mice, flies, fungus, plants and bacteria [99–103] but so far not in humans. Arrhythmicity at the organ or organism level may also result from uncoupled oscillators that drift out of phase (apparent or functional but not necessarily genetic arrhythmicity). Genetic ablation of neuropeptides such as VIP or its receptor, VPAC2, leads to arrhythmicity at the behavioural level despite many neurons remaining rhythmic (in the case of the VIP knockout [104,105]). Tumours of the SCN region also lead to arrhythmicity [45].

In Figure 3B, the circadian state of the SCN is represented by the larger symbol on the left. The state of peripheral clocks is shown as the smaller symbol(s) to the right of the larger symbol. If all tissues and organs adopt the same state then a single icon is indicated. If different tissues adopt different relative entrained phases (e.g., liver *versus* heart) then two icons are indicated. The numbers under the respective combinations refer to the states shown in Figure 3A. Table S1 in the Supplemental Information gives a more detailed description of the respective phase maps and — if known — lists their associated syndromes.

Some combinations of states are unlikely to occur and/or have so far not been reported in experiments. For instance, how could all peripheral clocks be arrhythmic when the SCN functions optimally (Figure 3B, Table S1; state 1-4/4)? This could theoretically

only be observed with genetic manipulations (e.g., an SCN tissue-specific rescue in an otherwise arrhythmic animal) and even then some tissues may become rhythmic. Other phase constellations are highly likely. Similar to 1-1/1 (representing optimal entrainment), 2-2/2 represents optimal entrainment for an extreme chronotype who is not challenged by social temporal constraints [106]. State 3-3, with all oscillators running free, has been shown in subjects in experimental temporal isolation as well as in N24 patients and in totally blind individuals [61,89,91]. This state may also develop in the presence of conflicting zeitgebers, where an extended amount of time is required for re-entrainment to a new phase, with a resultant drift towards a new phase [107]. If these individuals eat regularly, at socially dictated times, they would be better represented by phase map 3-1/3.

However, some combinations are likely although they have not been formally demonstrated. The combinations 1-1/4 and 2-2/4, with only certain tissues being arrhythmic, might represent certain tumours. Despite several established cancer lines showing self-sustained rhythmicity in constant conditions, cancer tissues may still be arrhythmic [108,109]. The basis therein may lie in the observation that cells from some colorectal cancers show rapidly damping rhythms [110]. Note that these are observations from constant conditions. If endogenous temperature cycles were present, even these rapidly damping cells might easily entrain.

The constellation 2-1/3 shows an abnormal phase of the SCN (e.g., an extreme early or late chronotype) with part of the periphery showing normal entrainment (e.g., the liver adjusted to customary, social meal times), while other peripheral oscillators run free. Oscillators near the limit of their range of entrainment, as would be predicted for extremely late or early entraining systems, will run free if their zeitgeber becomes too weak to hold them in the entrained state.

We would profit enormously in our understanding of 'clock and health' by establishing the phase maps in healthy controls under different entraining conditions and at different ages. We then could compare them to those that exist in syndromes related to challenged circadian systems: how are they distinct, what do they have in common, and what are the limits wherein health is not challenged? Unfortunately, quantitative methods to identify individual states in different tissues are largely lacking. Thus, reliable biomarkers that report entrained phases of various oscillators will be essential to make diagnoses and to evaluate treatments in chrono-medicine.

Concluding Remarks

At the outset of this review, we described that much of what is known concerning human health and the circadian clock comes from epidemiological associations. The causal mechanisms of this relationship have begun to be elaborated in experiments. The fact that the circadian programme and sleep are so tightly coupled and that both may have an individual role in balancing health and disease (Figure 2) complicates the search for mechanisms even further [39]. The insight that misalignment between different elements of the circadian programme is at the basis of the mechanisms linking clock and health is becoming increasingly clear [111–114]. The path forward, then, would involve describing the entire surface of alignments — the constellation of phases — to establish normal distributions therein. At that point, protocols to detect sub-optimal entrainment can be established and the use of zeitgebers to return to optimal entrainment can be developed, e.g., in dedicated circadian clinics [113].

We propose a four-point plan to implement chronobiological principles into medical practice — a roadmap towards an evidence-based chrono-medicine.

Differential Diagnosis

Our taxonomy describing the entire surface of possible constellations of circadian states (Figure 3B) calls for systematic, basic research. First, we need to develop a set of biomarkers that robustly and cheaply report on the circadian states (Figure 3A) in everyday life. These will be used to determine the states of the pressure points of clock and disease: SCN, metabolism, the immune, endocrine, cardiac and digestive systems and cognitive functions. The circadian system, predisposition and vulnerability to pathologies as well as their combination are all highly individual. One therefore has to collect data from many different individuals of different ages, at different seasons living in different environments (urban vs. rural) to produce a meaningful database of phase maps. As epidemiology links health states and misalignments, chrono-medicine has to establish how misalignments relate to different phase maps by comparing healthy day workers without SJL with shift workers, trans-meridian travellers and those suffering from chronic SJL. The results will help to distinguish between tolerated and high risk constellations. Franz Halberg measured the daily time courses of many different functions, tissues and patients for more than 50 years [115], resulting in more than 3,000 publications. His work underlines how much medical measurements are impacted by the circadian clock but it never produced the systematic, context-embedded overview we envision here.

Development

Chrono-medical treatments logically should work towards realignment of optimal phase maps (despite that we do not yet know the normal distribution therein). This can be achieved via at least three approaches in addition to the use of zeitgebers: pharmacology, technology and socio-political. If our thoughts about the circadian system's possible states, phase maps, and their aetiologies are correct, we will need to develop agents that can differentially reset different parts of the system, that can increase eigen-zeitgeber strength, increase the sensitivity of a tissue to its eigen-zeitgebers or increase coupling of the oscillators within a tissue. On the technological side, we have to extend the already on-going development of strengthening light environments (more light during the day and less light during the night). The solutions will take advantage of dynamic changes in spectral composition, and of architectural solutions to get more daylight into buildings. The socio-political approach has to foster chronotype-based tailoring of work-schedules beyond the shift-work context [116], which will need an entire new approach to work-related legislation.

Treatment

Once the pharmacological, technological and socio-political methods and changes are developed and the surface of phase maps is established, chrono-medicine will have a powerful toolbox at hand to develop personalised treatment plans. They will involve prescribing specific zeitgeber exposures

(ranging from timing, amount, and spectral composition of light to specific times for meals or exercise), changing work/school schedules, recommendations for lighting at the workplace and at home. If these less invasive treatments don't work, chrono-medicine will also extend to prescribing the drugs mentioned above which will give chrono-pharmacology a new dimension. Traditionally, chrono-pharmacology determines the optimal times-of-day for specific drugs that are already on the market [117]. Since the clock regulates about half of the known targets of the best-selling drugs worldwide [118], side effects can be minimised while primary effects maximised by tuning the drug's timing.

Education/Prevention

We have to develop education packages that will be part of all medical training programmes — from doctors and nurses to therapists. Other educational packages have to be developed for architects, light manufacturers and light planners. We have to also change the awareness of management and policy-makers towards supporting personalised work schedules and of politicians to understand the consequences of DST.

SUPPLEMENTAL INFORMATION

Supplemental Information includes one table and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2016.04.011.

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