



GUEST EDITORIAL

Chronobiology and psychiatry

We can begin with the ancient Greeks, meander through Latin footnote-sprinkled chapters in the 1621 *Anatomy of Melancholy*, and dive into the writings of late nineteenth century German psychiatrists. All describe daily and seasonal cycles in many aspects of mental illness. Depression in particular is linked to characteristic rhythm abnormalities: diurnal mood variation and early morning awakening, longer-term periodicities such as regular manic-depressive cycles or seasonally linked episodes.¹ But it was very difficult to connect these clinical observations over the centuries in any heuristic manner to an underlying biological timing system, lacking grounding in circadian biology, a field which only began its modern development in the 1960s.² One could observe altered rhythms, but there was no theoretical construct to explain them. It was primarily the pioneering work of Jürgen Aschoff and Colin Pittendrigh that gave us a rigorous framework for understanding temporal behaviour. Today, not only has the existence of a central circadian pacemaker (localised in the suprachiasmatic nuclei) been established, but also peripheral clocks are found in every organ and every cell.³ Zeitgebers (synchronising agents) are required to reset and stabilise these central and peripheral clocks—the light–dark cycle is the major zeitgeber, but social cues, mealtimes, exercise, etc. play a complementary role. Growing understanding of the complex feedback loops in clock gene expression that create “the day within” reveal how a mutation or polymorphism at the molecular level can be pathological: mice with a CLOCK mutation manifest behaviour that is strikingly similar to human mania⁴; two family pedigrees of advanced sleep phase syndrome have a hPer2⁵ or CK1δ mutation ...⁶

In 1976, Pittendrigh and Daan wrote five papers that expounded the formal properties of circadian rhythms.⁷ Reading these was an extraordinary

experience. It was as if there was suddenly a scientific language in which to express the clinical observations, a framework for formulating experiments. Tom Wehr and I called it Pittendrighian psychiatry, attempting to understand underlying rules by which, for example, manic-depressive patients shifted circadian phase earlier and later according to clinical state.⁸ According to our theory, if we simply phase advanced the sleep–wake cycle of a bipolar depressed patient, we could improve depression. Indeed, the effect of this circadian manipulation was remarkable.⁹ The patient’s diurnal rhythm of mood shifted day by day across the window of waking, a kind of jet-lag with positive clinical response—but depression returned as she slowly re-entrained. We rephrased the Pittendrighian “internal coincidence model” to apply to these “depressogenic” phase relationships.¹⁰

Later, the concepts of adequate zeitgebers, phase response curves to light, and dawn and dusk oscillators responding to daylength (photoperiod) were crucial in the development of light therapy to treat seasonal affective disorder (reviewed in Ref. 11). It is remarkable how fruitful has been this hypothesis-driven therapy based on neurobiological concepts, inspiring elegant studies of mechanism. Clinical trials by many researchers have tested the antidepressant response to different paradigms: extension of the photoperiod to simulate a summer day, early morning light to phase advance the circadian pacemaker, and dose-intensity-duration (and recently, spectrum) of light exposure. Yet, since these are not typically the classical clinical trials of “placebo” light vs. “active” light, they do not fulfil criteria for inclusion in conventional meta-analyses—in spite of the fact that the quality of clinical research is as high as one could wish (see Terman’s review in this issue¹²).

In 1982, Borbély developed a two-process model of sleep regulation.¹³ For the first time, the

circadian system was integrated into sleep research, and considered important as determining timing and architecture of sleep by virtue of its interaction with homeostatic drive. For someone working in psychiatry, this was a fascinating concept, in particular because Basel was one of the first clinics in the early 1970s to investigate the remarkable and counterintuitive antidepressant effect of a single night's sleep deprivation in patients with major depression.¹⁴ This paradoxical intervention improved depression within hours, but how or why was a mystery. We tried to apply the two-process model to understand how sleep deprivation could be antidepressant.¹⁵

These models were an amazing stimulus to basic research, and they remain so. However, they remain less recognised in clinical psychiatry. If the literature on circadian rhythms in depression is reviewed,¹ the evidence points to a variety of changes—disturbances of phase (early or late), reduced rhythm amplitude, and increased day-to-day variability, rather than any single or specific phase disturbance as predicted by our original hypotheses. Individuals vulnerable to depression are vulnerable to changes in sleep duration and timing.

We still do not know how sleep deprivation works, though in rodents it can diminish amplitude of the circadian pacemaker in the suprachiasmatic nuclei,¹⁶ as well as many downstream circadian neurotransmitter rhythms.¹⁷ A lower amplitude rhythm can be more easily shifted and reentrained. After a 20-year hiatus (sleep deprivation does not fit the current psychopharmacological zeitgeist), a new generation of clinician researchers has begun using sleep deprivation again, combining the advantages of its rapidity of onset (that no drug can yet approach) with medication and/or light to maintain the usually short-term response (see Benedetti et al.'s review in this issue¹⁸). We still do not know how light works, but our models predict the importance of a strong zeitgeber for appropriate synchronisation of central and peripheral clocks. Strong entrainment appears to be the key to good behavioural, cognitive and emotional well-being—not only in depression (Table 1). We have shown that even in healthy subjects, a small misalignment of sleep with respect to the circadian system (internal phase angle difference a little more than an hour), can increase sleepiness and diminish mood.¹⁹

This special issue of *Sleep Medicine Reviews*, "Chronobiology and Psychiatry" covers a broad domain of sleep medicine impinging on and becoming an integral part of psychiatry.²⁰ The first three reviews address basic aspects of human

Table 1 Circadian rhythms and psychiatry: what is important?

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- Stable internal and external phase relationships
- Appropriate entrainment to the light–dark and sleep–wake cycle
 - Enough light, enough darkness
 - Adequate retinal function
 - Sufficient social zeitgebers
 - Reconsider the zeitgeber function of timed activity and meals
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circadian rhythms and sleep, with results that are immediately clinically relevant.

Till Roenneberg et al.²¹ have taken the original concept of morningness and eveningness preferences and further developed it into a questionnaire that asks how and when people actually sleep on work and free days. Importantly, the analyses recognise the interactions of chronotype with external zeitgebers, correcting for sleep deficit during the week and rebounds over the weekend to better estimate an individual's sleep duration. As a web-based tool now available in many languages, the questionnaire has the advantage of large numbers permitting epidemiological-type analyses.²² Chronotype is genetically based, but modified by age and sex. It is well known that teenagers sleep late, but with this questionnaire the delay shift could be quantified—drifting later 15 min/year from age 12–20 and thereafter slowly advancing back in old age. The pattern was observed in rural as well as urban areas, suggesting a biological rather than social phenomenon—more evidence supporting political (and health) demands that teenagers' school times should be later! It is the extreme late chronotypes who have the greatest problems (as detailed in Ref. 23 in this issue), for which Roenneberg and co-workers have coined the colourful and immediately comprehensible term "social jetlag".²⁴

Our Basel lab has been fortunate in having had close connections with one of the fathers of circadian biology, Jürgen Aschoff, during his last years in Freiburg. He was particularly supportive of and interested in the constant routine thermoregulatory studies developed by Kurt Kräuchi. Kräuchi's review in this issue²⁵ pays homage to Aschoff's pioneering concepts and experiments, providing a concise introduction to how the circadian system regulates temperature rhythms, as well as a convincing argument against direct involvement of temperature in sleep homeostasis. Many experiments tease out the crucial role of distal skin temperature (hands and feet) as being

the “physiological gate” to sleep onset. Warm feet promote a rapid sleep onset, cold feet prevent it. Individuals with vasospastic syndrome have a circadian sleep disorder, caused by going to bed too early with respect to the circadian system’s readiness to fall asleep (delayed by about an hour). Perhaps other sleep onset disorders may arise from problems in this circadian thermophysiological cascade (e.g., age- or stress-related changes in vasomotion, vasoconstricting side-effects of medications). This research provides a scientific rationale for unabashedly reviving all the old-fashioned non-pharmacological treatments that help warm the feet (hot baths, bedsocks, warm drinks, relaxation techniques, etc.) and using them in the everyday practice of sleep medicine for many sleep onset disorders.

A new era of studying the biological effects of light in humans was introduced by Lewy’s finding that light suppresses melatonin.²⁶ Since then, elucidation of the human phase response curve to light has provided the scientific basis for using light to treat winter depression and sleep–wake cycle disorders. Cajochen reviews an additional important aspect—light’s direct, rapid alerting effects in addition to its zeitgeber function.²⁷ It is clear that both subjective sleepiness and the EEG/EOG-correlates thereof are affected by light intensity, timing, duration, and spectrum (short-wavelength blue corresponding to the participation of non-visual melanopsin-containing photoreceptors). We do not yet have a phase-response curve to the alerting effects of light; to have one would be useful for future applications in the work place or on night shift, and indeed would provide a new approach to architectural lighting solutions necessary for enhancing neurobehavioural performance.

Van Someren and Riemersma-Van Der Lek have put together a very provocative case for the importance of regular, strong 24-hour zeitgebers for health and well-being.²⁸ They move beyond theoretical circadian principles to application in the field, with an emphasis on stabilising sleep timing. The circadian clock diminishes in amplitude and precision with age, and more so in Alzheimer’s disease. The resultant worsening of the sleep–wake cycle affects cognitive performance and mood. The important message from the Dutch group has been for years, “Use it or lose it.” Can we make up for loss of clock function by increasing zeitgeber strength, establishing regular 24-hour patterns of behaviour (exercise, meals, going outdoors for sufficient light exposure, sleep times)? Their new double-blind study of 3.5 years light and/or melatonin augmentation in Alzheimer’s patients is the first to show that the degenerative process can

be slowed down—a very important clinical trial. The findings emphasise the necessity of *long-term* regular chronotherapeutics. Their concepts are applicable to many psychiatric and other sleep–wake cycle disturbances (Table 2).

Okawa and Uchiyama review the specific hypotheses and entrainment pathology of delayed sleep phase syndrome (DSPS) and non-24 sleep–wake disorder,²³ clearly indicating multiple aetiologies. There are many ways to get to DSPS—from genetic predisposition to lack of morning light exposure, too much evening light, or combinations thereof. One of the most important messages is that these circadian sleep disorders can coexist with psychiatric conditions—DSPS is often associated with personality disorders and DSPS can lead to depression. Conversely, many psychiatric conditions accompanied by social (and consequently light) withdrawal may lead to abnormal sleep–wake cycles. Over many years of actimetry, we have found a wide variety of circadian abnormalities in psychiatric inpatients—not specific, but contributing to symptoms of the particular diagnosis. The better entrained the rhythms, the better the cognitive function and negative symptoms in schizophrenic patients,²⁹ the less the self-injurious behaviour in borderline personality disorder³⁰ (Table 2).

Terman reviews a respectable body of evidence for light being equally effective as an antidepressant in both SAD and non-seasonal major depression.¹² His tantalising and impressive case histories of previously treatment-resistant, chronic or recurrent depressive patients who respond well to adjunctive light are hopefully a prelude to an entire reconsideration of light as a major therapeutic tool. Important, in this circadian treatment paradigm, is that light administration be carefully timed according to individual chronotype, which can now be assessed online.³¹ One can even speculate that if poor circadian synchronisation is a cause of, contributes to, or exacerbates depressive symptoms, then correct timing of antidepressants (i.e., their use as a zeitgeber) would be required for optimum efficacy. Such a treatment

Table 2 Circadian rhythms and psychiatry: simple practical rules

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| The first law of chronobiology in medicine Entrainment = rhythms better—sleep better—think better—feel better—behave better |
| The second law of chronobiology in medicine Entrainment needs sustained regular zeitgebers more light! more darkness! |

strategy has not ever been considered. Would, for example, the multicentre study of antidepressant supplements to mood stabilisers in bipolar depression have yielded a better result had timing been considered?³² What Terman's case studies suggest is that the correlates of depressive behaviour—lack of zeitgeber signals due to social and environmental withdrawal—may impact negatively on stability of entrainment. If so, a solution would be to prescribe light therapy for *all* forms of depressive illness. His clinical examples are the tip of a huge iceberg. I predict that light therapy in all its forms (light boxes, dawn simulators, architectural lighting solutions, awareness of spending time outdoors in natural light) will become a major treatment approach for many more symptoms than “just” low mood and many more sleep disturbances than “just” circadian. Additionally, many patients prefer to be treated with light, which has distinctly fewer side effects than medication.

The chronotherapeutics group in Milano have not waited for consensus statements, meta-analyses, or psychiatric-association guidelines to get down to work in everyday practice. For more than 10 years, Benedetti et al.¹⁸ have applied non-pharmaceutical clinical interventions—sleep deprivation (or wake therapy), sleep phase advance, light and dark therapy—on a psychiatric ward. This real-world setting is paired with chronobiological research flair, and their pragmatic approach—if it works, use it, improve it, see if it can promote long-term changes in psychopathological conditions—has been justified by results that repeatedly document efficacy, rapidity, and lack of side effects. The transient improvement after sleep deprivation can be stabilised by combining chronotherapeutic techniques. Continued remission rates at 9 months are comparable to those obtained with long-term antidepressant treatments. Sleep deprivation has been established as the treatment of choice for hard-to-treat bipolar depression—not only by the psychiatrists, but also by the governmental health authority in Lombardy. Should not medical insurance companies be interested a method that gets patients out of depression fast? Sleep deprivation and light therapy have attained the status of powerful and affordable first-line clinical interventions for treating major depression.³³

This dense, speculative and databased, original and creative set of papers reflect the excitement of the field—circadian research is in an unprecedented high. They reflect clinical expansion—not only is chronotherapeutics applicable to the original circadian sleep and mood disorders, but also light therapy may be efficacious in any neurological, psychiatric, or medical disorder

where entrainment of the sleep–wake cycle has gone awry, where zeitgebers are weak or irregular. There are a lot of disorganised sleep patterns out there in clinical medicine—we do not know half of them.

It is perhaps difficult for doctors to move from a “light-therapy-is-for-winter-depression” mind-set to considering the broad potential of light to help patients improve sleep–wake cycle disorders within the context of any diagnosis—whether aftereffects of whiplash injury or post-operative cardiac patients. Read these reviews—and try it out!

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