Review

Health in a 24-h society

Shantha MW Rajaratnam, Josephine Arendt

With increasing economic and social demands, we are rapidly evolving into a 24-h society. In any urban economy, about 20% of the population are required to work outside the regular 0800–1700 h working day and this figure is likely to increase. Although the increase in shiftwork has led to greater flexibility in work schedules, the ability to provide goods and services throughout the day and night, and possibly greater employment opportunities, the negative effects of shiftwork and chronic sleep loss on health and productivity are now being appreciated. For example, sleepiness surpasses alcohol and drugs as the greatest identifiable and preventable cause of accidents in all modes of transport. Industrial accidents associated with night work are common, perhaps the most famous being Chernobyl, Three Mile Island, and Bhopal.

The 24-h society is an environmental challenge that outstrips our biological adaptation to the natural 24-h cycle of light and darkness. In the course of evolution, the behaviour and physiology of most organisms, including human beings, have developed internal temporal characteristics. It is thought that by timing behaviours such as sleep so that they complement the organism's spatial ecological niche, internal stability is maintained and the chances of an organism's survival are increased.

The effects of 24-h shift operations on sleep and general health have been the topic of much research during the past 2 decades. Night-shift workers, for example, have poorer daytime sleep, reduced night-time alertness and performance, and an increased accident rate compared with those on day shift.[1–4] Prominent health problems among shiftworkers include sleep disorders (which can become chronic), gastrointestinal disease, increased incidence of cardiovascular disease, lipid intolerance evidenced by increased triacylglycerol concentrations, and possibly an increase in late-onset diabetes.[5,6] In addition to health problems there is a substantial cost to the economy in terms of decreased efficiency and productivity. The cost of sleepiness-related accidents can vary substantially, but in general, the estimated total cost of such accidents per year is US$16 billion in the USA, and US$80 billion worldwide.[7]

Time-of-day influences

More than a century ago, it was reported that the capacity for doing mental work varies throughout the day. Several empirical studies have revealed time of day variations in performance, with subtle differences between different tasks.[8] Similarly, in participants that are exposed to 36–60 h of sustained wakefulness in controlled laboratory (or constant routine) conditions, significant time of day variations in task performance are reported, with performance being worst for all tasks just after the time of core body temperature minimum (about 0400–0600 h).[9] Subjective alertness levels are closely related to the time-of-day variation in task performance (figure 1).

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Centre for Chronobiology, School of Biomedical and Life Sciences, University of Surrey, Guildford GU2 7XH, UK (S M W Rajaratnam PhD, Prof J Arendt PhD)

Correspondence to: Prof Josephine Arendt (e-mail: j.arendt@surrey.ac.uk)

In the UK, as in many other countries, sleep-related vehicle accidents peak in the second half of the night (0200–0600 h), and also show a very modest rise in the mid afternoon (1400–1600 h).[10] The modest rise in accidents in the mid afternoon (which is small compared with the nocturnal rise) could reflect the post-lunch decrement in performance.[8] When variation in traffic density is taken into account, the likelihood of a sleep-related vehicle accident is 20 times higher at 0600 h than at 1000 h. Similarly, the risk of injury and fatality during the night shift is significantly greater than it is during traditional daytime working hours.[4,11] The cause of such accidents and injuries is often multifaceted, and the precise contribution of sleepiness is difficult to estimate.

One of the major influences on time-of-day variations in physiology and behaviour is the activity of internal rhythm generating systems. Circadian (about 24 h) rhythms, are controlled by a master biological clock. In mammals, the master biological clock is located in the suprachiasmatic nuclei of the hypothalamus.[12] At the subcellular level of organisation, circadian rhythms are generated by transcriptional and translational feedback loops involving multiple clock genes.[13] The precise periodicity (or cycle length) of the biological clock is known to be genetically determined,[14] and variation in clock genes is thought to be related to individual differences in natural wake and sleep times.[15]

The biological clock generates and maintains circadian rhythms in most physiological, biochemical, and behavioural variables—for example, core body temperature, triacylglycerol, blood pressure, sleep-wakefulness, alertness, mental performance, and the synthesis and secretion of many hormones including melatonin, cortisol, prolactin, and growth hormone (some of these are shown in figure 1). A reliable and extensively researched marker of biological-clock activity is the rhythm of melatonin. Melatonin is the principal hormone of the pineal gland. It is synthesised and secreted at night in both day-active and night-active species, thereby acting as a signal for the length of day and night. In human beings, sleep is normally initiated during the rising phase of the melatonin rhythm and declining phase of the body temperature rhythm. Attempts to sleep at inappropriate phases of the circadian cycle, for example during the declining phase of melatonin and rising phase of body temperature, will usually result in shorter sleep episodes and more awakenings.[16] Such attempts are frequent in workers on night shifts.

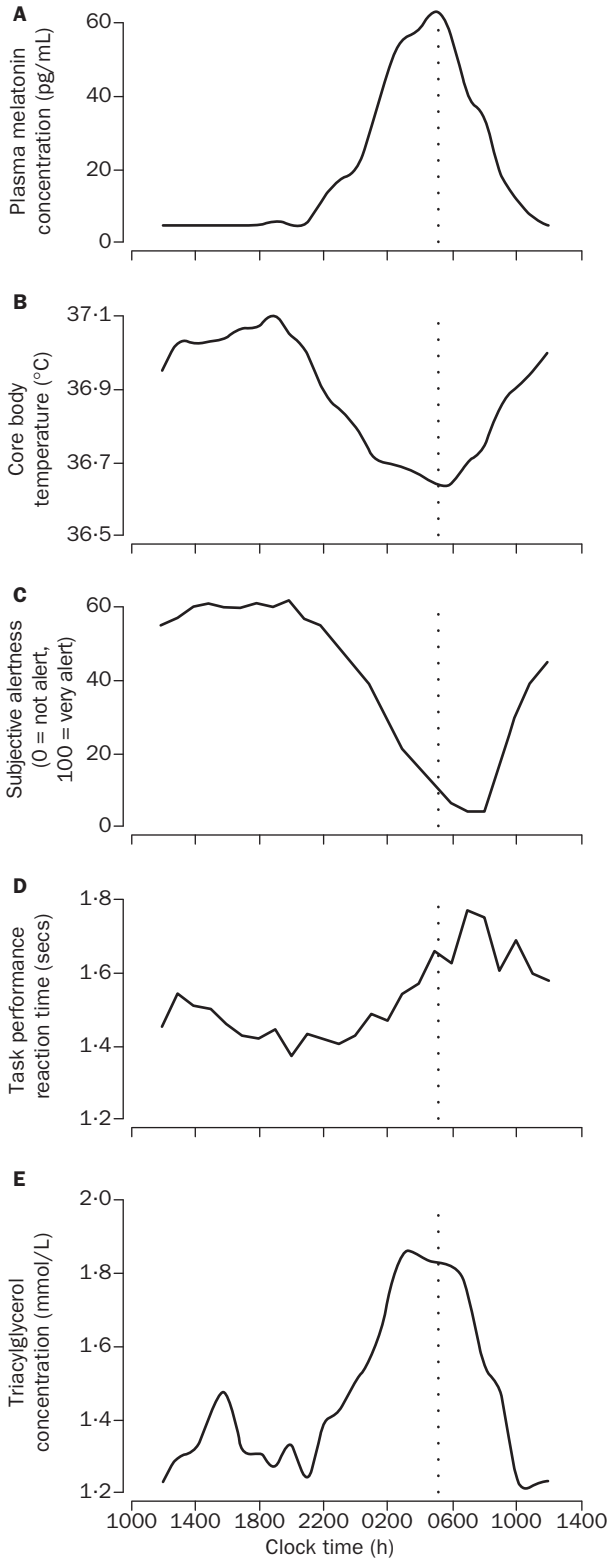

Figure 1: **Circadian rhythms of plasma melatonin, core body temperature, subjective alertness, task performance (reaction time, in secs), and triacylglycerol, from human beings held in constant routine conditions (ie, controlled light, posture, activity, and meals)**

The peak in the melatonin rhythm (panel A), shown by the dotted line, and the low-point of the temperature rhythm (panel B) are within 1 h of each other. The low-point of the alertness and performance rhythms (panels C and D, respectively) is shortly after the melatonin peak, and the peak in triacylglycerol (panel E) coincides with the melatonin peak.

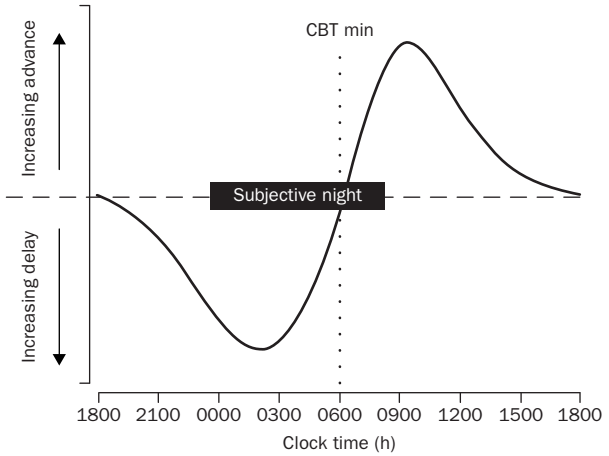

Figure 2: **Phase response curve (PRC) of a human being, in response to light**

Subjective night (ie, night-time according to the biological clock) is indicated by a black horizontal bar. Maximum phase shifts are within 4–5 h of the time of core body temperature (CBT) minimum. The precise shape and amplitude of PRCs for human beings depends on the strength (ie, intensity and duration) of the light stimulus.[18]

Light is the major synchronising agent for mammalian circadian rhythms. Results of studies have shown that exposure to even low light levels (100 lux), similar to that found in offices and living rooms, will substantially affect the phase of human circadian rhythms.[17] However, without scheduled activities and sleep, such intensities seem incapable of maintaining optimum synchronisation to the 24-h day.

Responses to light depend on the time of exposure in relation to the internal biological clock: exposure to light just after the body temperature minimum will advance the phase of circadian rhythms, whereas exposure before the body temperature minimum will induce delays.[18] Core body temperature is usually at a minimum around 0400–0600 h, but it can be substantially displaced by shiftwork, jet-lag, and other situations. Time of day-dependent responses are usually described according to a phase response curve (PRC; figure 2). PRCs can be used to predict the timing of light treatment to enable adaption to environmental changes, such as those seen in shift-work and transmeridian travel.

In continuous darkness or in dim domestic intensity light and in the absence of other important time cues such as an imposed sleep-work schedule, human rhythms free run, or become desynchronised from the 24-h day and express the underlying periodicity of the biological clock. This is often seen in blind people who have no conscious light perception.[19] Rhythms can be synchronised by weak time cues, but have an abnormal phase relation with the environment.[20] An example is the tendency to oversleep in winter (dim light), which in polar regions (especially in individuals with no behavioural impositions such as scheduled sleep wakefulness and work times) can become an overt free run.[21] For those working indoors during a normal day (0800–1700 h), bright natural early morning light is only seen in the summer in the higher latitudes of temperate or polar regions, and this early morning light exposure might well result in earlier circadian phase.

Timed exercise can also shift the human biological clock, however, to date mainly phase delays have been shown.[22] Appropriately timed administration of melatonin can, in addition to inducing sleepiness, phase shift and synchronise the human circadian system.[23,24] In countries where melatonin is freely available, it is extensively,

indiscriminately, and no doubt often inappropriately, used as a treatment for circadian rhythm disorders and as a sleeping pill.[25]

Shiftwork and jetlag

A key characteristic of the biological clock is its ability to re-adjust (either by phase advancing or delaying) to changes in the environment, for example after transmeridian travel. On average, the clock shifts about 1 h per day in the absence of countermeasures.[26] Symptoms of jetlag are thought to be caused by desynchronisation of circadian rhythms from the external environment, the transient change in the phase relationship of individual rhythms,[26] and perhaps changes in the amplitude of rhythms.

About two-thirds of travellers report having jetlag. Symptoms of jet-lag include daytime tiredness, difficulty initiating sleep at night (after eastward flight) or early awakening (after westward flight), disturbed night-time sleep, impaired daytime alertness and performance, gastrointestinal problems, loss of appetite, and inappropriate timing of defecation and urination.[26] Such symptoms can seriously impair a person's performance and ability to function, in part because of the reduction in sleep quality and quantity, and because performance and alertness rhythms will take several days to resynchronise. In the long-term (eg, after 4 years), chronic disruption of circadian rhythms from regular transmeridian travel might result in cognitive deficits (decreased short-term memory, slower reaction time) and changed physiological parameters (such as cortisol concentrations).[27]

Because of their rapidly changing and conflicting light-dark exposure and activity-rest behaviour, shiftworkers can have symptoms similar to those of jetlag. Although travellers normally adapt to the new time zone, shift-workers usually live out of phase with local time cues.[28]

Shift-work schedules are generally classified in terms of the speed (rapid or slow) and direction (forward or backward) of rotation. The issue of which schedules are preferable from the perspective of sleep and biological rhythm research is contentious.[1] On the one hand, in rapidly rotating schedules, which incidentally are rarely used in North America, the biological clock maintains a normal phase and workers are thus able to continue their conventional activities during off-duty days without symptoms of internal desynchrony. However, the problem with such schedules is that shifts can, and often do, coincide with the time of day when the biological drive for sleepiness is high and performance is low. By contrast, a slow rotation schedule is conducive to circadian adaptation. During days off duty, workers typically revert to the conventional day-active pattern. In Antarctica and in one North Sea oil rig shift schedule (figure 3) complete adaptation is found, but such situations are rare.[29,30] In the offshore situation, many more complications are seen in sleep and performance in the rollover shift than with 2 weeks of night shift.[31] The theoretical notion of directional asymmetry in circadian adaptation to rotating shift schedules is based on the same principles as for time zone travel; forward (clockwise) shift rotation would result in more rapid adaptation than backward rotation. To date, however, field studies have failed to conclusively show that backward rotation is more detrimental than forward.[32]

In addition to disruption of sleep, abrupt changes in time cues might have negative effects on other physiological systems. Compared with the effects of sleep, few studies have examined the effects of shiftwork on cardiovascular, digestive, immune, and reproductive systems, all of which are rhythmic in nature.[26]

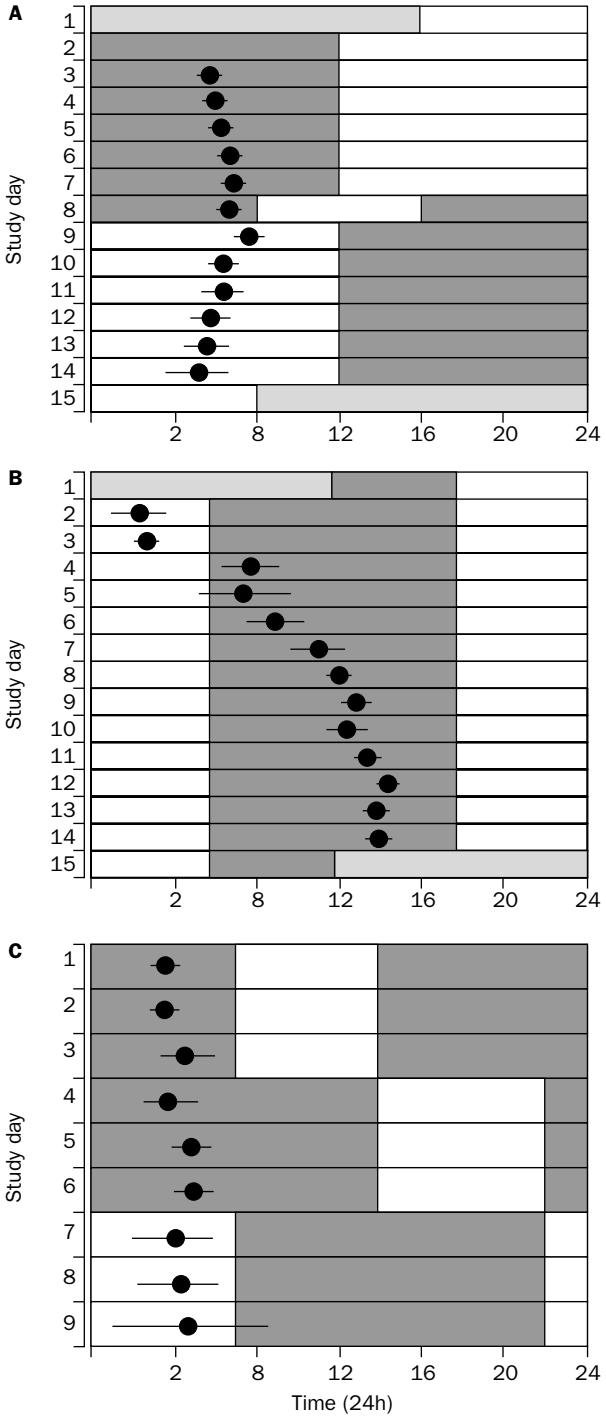

Figure 3: **Three types of shift schedule showing variations in the behaviour of the internal clock during shiftwork**

Schedules A and B are used on North Sea oil rigs, schedule C is an onshore factory schedule. The darkly shaded portions are free time or sleep, the unshaded portions are work time and the lightly shaded areas (schedules A and B) precede and succeed the time offshore. The peak of the melatonin rhythm, assessed by measurement of its major metabolite in sequential urine samples on each day of each schedule, is shown by the filled circles (mean [SE]) and is the phase of the circadian clock. (Schedule A) rollover shift, days 2–7 are dayshift (work time 1200–2400 h), day 8 change over day, (work time 0800–1600 h), days 9–14 nightshift (work time 2400–1200 h). (Schedule B) days 0–14 night shift (work time 1800–0600 h). (Schedule C) days 1–3 early shift (work time 0700–1400 h), days 4–6 late shift (work time 1400–2200 h), days 0–9 night shift (work time 2200–0700 h). The circadian clock adjusts fully to the displaced sleep and work time only in the schedule shown in B: the melatonin rhythm shifts such that the peaks are seen during the mid-sleep period during the day.[31]
Panels A and B: data are redrawn from references 30,33 with permission.

Epidemiological studies are problematic; we know that people who are intolerant to shiftwork tend to select themselves out of such occupations. A review of studies[34] that investigated shift work and risk of cardiovascular disease claimed that on balance, shift-workers have a 40% increase in risk. Investigators have shown that meals taken during biological night (or during an unadapted night shift) lead to higher plasma triacylglycerol concentrations (an independent risk factor for heart disease) than identical meals taken during the day, which might in part explain the increased occurrence of cardiovascular disease among shiftworkers.[35,36] Glucose tolerance is also known to deteriorate in the evening,[37] and there is evidence that increased peripheral insulin resistance might contribute to this effect.[6] Resistance to insulin is a putative risk factor for cardiovascular disease and type 2 diabetes mellitus, and again, this could explain the raised incidence of disease among shiftworkers.

Strategies have been developed to enhance circadian adaptation to shift-work schedules and time zone changes. Factors that promote sleep hygiene are advised, such as adequate sleep, sleep in a quiet and dark environment, control of the use of caffeine and alcohol, and timing sleep (with or without the use of hypnotic agents) to the desired sleep time relative to the new time zone or shift schedule. As described earlier, exposure to light can phase shift circadian rhythms. Therefore, scheduled bright light exposure and avoidance of light (possibly by use of dark goggles) might be useful in accelerating adaptation.[38] Most field studies and laboratory-simulated phase-shift studies report that correctly timed administration of the hormone melatonin is also able to moderately shorten the time taken for circadian adaptation.[26] However, there is little evidence for optimum dose or formulation, and there is no information on long-term safety. Further research is needed to examine how combined administration of bright light and melatonin could be used to develop effective, reliable, and practical treatment strategies.

It is not always desirable to adapt the circadian system to new shift schedules, for example in rapidly rotating shifts, because sleep and activity on rest days will be compromised. Similarly, when travel to a new time zone is for a short time (eg, 1 or 2 days), circadian re-adaptation might not be worthwhile. In such cases, short-term strategies can be used to maintain alertness and performance, especially during early morning hours, and to improve sleep, without shifting the biological clock.

Sleep loss and sleepiness

Sleep loss is obviously the most important immediate consequence of night work. In general, sleep loss will result in performance deficits, including increased variability in performance, slowed physical and mental reaction time, increased errors, decreased vigilance, impaired memory, and reduced motivation and laxity.[39] There is no consensus on the extent of impairment resulting from a given amount of sleep loss.

Depending on the performance task measured, after 17–19 h of sustained wakefulness, decrements in task performance are equivalent to, or worse than, those seen at a blood alcohol concentration of 0·05%,[40] and about 20–25 h of wakefulness will result in performance decrements equivalent to a blood alcohol concentration of 0·10% on some tasks (figure 4).[41] Generally, complex performance tasks seem to be more sensitive to the effects of sleep loss than simpler tasks. It is of interest to note that the legal blood alcohol concentration limit for driving in the UK, USA, and Canada is 0·08%, in Australia is 0·05%, and in Sweden is 0·02%. The decrements in

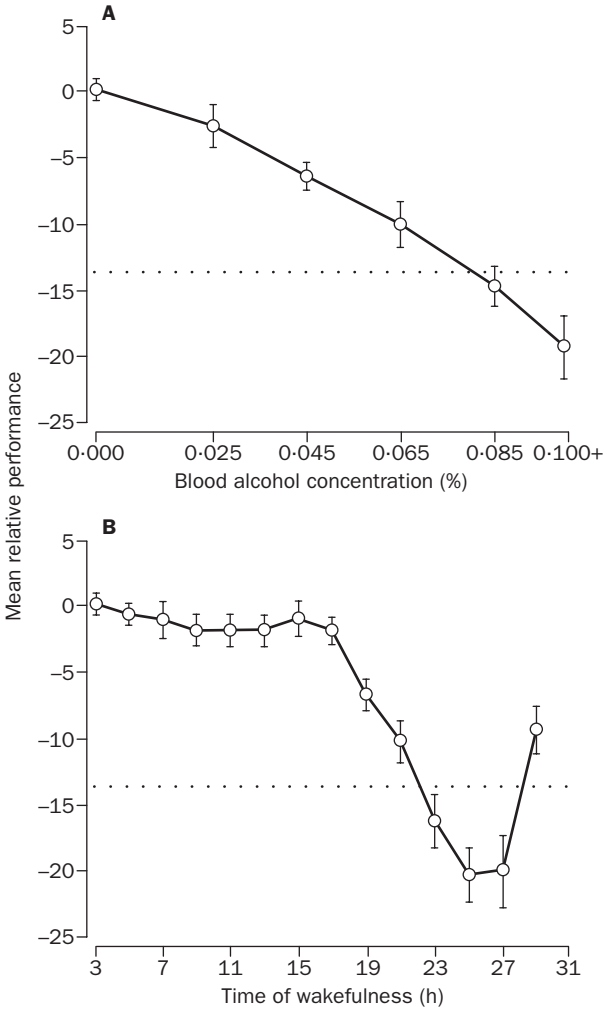

Figure 4: **Comparison of the effect of blood alcohol concentration (BAC) and hours of wakefulness on task performance**
Higher scores indicate better performance. The decrement in mean performance at blood alcohol concentrations of 0·10% or greater is similar in magnitude to those observed in after 25–27 h of wakefulness. Redrawn from Lamond and Dawson[50] with permission. (Panel A) Effect of blood alcohol on task performance. The dotted horizontal line is the mean performance at a blood alcohol concentration of 0·08% (the legal limit for driving in the UK). (Panel B) Performance is likely to be affected by circadian factors and sleep debt, thereby accounting for the recovery in performance after 27 h of wakefulness (about 1100 h in this experiment)

performance recorded after extended wakefulness have important implications for shiftwork, since a substantial number of shiftworkers are reported to be awake for at least 24 h on the first night shift in a roster.[42]

In reality, the temporal pattern of alertness and performance is thought to be the result of an interaction between circadian and homoeostatic influences (figure 5). The homoeostatic aspect, also referred to as sleep debt or sleep pressure, will increase as a function of the duration of wakefulness and dissipate during a subsequent sleep episode. Models have been developed to predict alertness levels as a function of these two factors.[43,44] Such findings can be usefully applied to shiftworkers to determine optimum sleep-wake schedules which keep alertness and performance at a maximum during the shift.

Effects of chronic sleep debt on metabolic and endocrine function have been reported.[45,46] Glucose tolerance and thyrotropin concentrations were found to be lower when participants showed sleep debt compared with when they were fully rested.[45] Evening cortisol

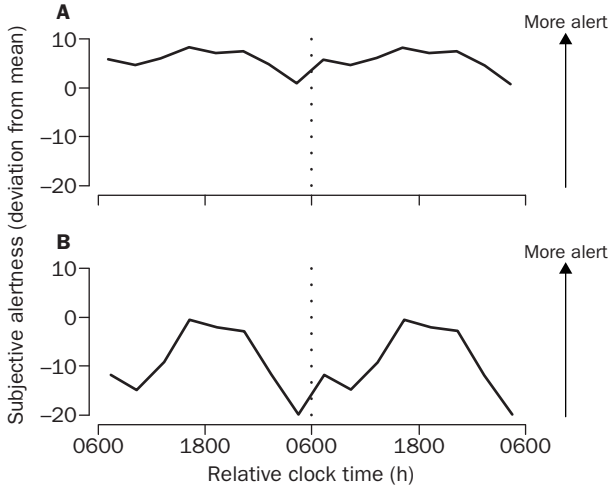

Figure 5: **Double plot (48 h) of the interactive effects of sleep debt and biological clock time on subjective alertness ratings.**
Alertness was assessed at various times of the day. For each assessment, sleep debt (the duration of wakefulness preceding the assessment) was either less than 3 h (panel A) or between 16 and 19 h (panel B). The dotted vertical line at 0600 h is the time of core body temperature minimum in these participants. In both A and B, minimum alertness is just before 0600 h. However, in B, the average level of alertness is substantially lower, and the rhythm amplitude is greater. Clearly, with increasing sleep debt the circadian influence is more pronounced. Redrawn from Dijk[43] with permission.

concentrations were raised in the sleep debt condition, and activity of the sympathetic nervous system was also increased—suggesting that sleep loss per se (even without circadian disruption) could have harmful effects on general health.

Several laboratories have been investigating the efficacy of different countermeasures to sleepiness, such as bright light exposure,[46] administration of caffeine[10] and other stimulant drugs,[47] and napping.[10] Exposure to bright light seems to be effective, however the optimum spectral characteristics, duration, timing, and intensity of light remains to be resolved. Many studies report that a nap, taken before, during, or after extended wakefulness or sleep loss, can be beneficial. The beneficial effects of napping on subsequent performance are not negligible; a short nap (<15 mins) in the mid-afternoon after restricted sleep on the previous night substantially reduced major and minor driving incidents in a car simulator to a similar degree to caffeine (150 mg, about 2·5 cups instant coffee), but only in participants who were able to sleep. When countermeasures to sleepiness are combined, such as caffeine (150 mg) followed by a short nap (<15 mins), the beneficial effects on performance can be greater than the individual treatments alone.[10]

An important issue associated with napping is sleep inertia, which is the feeling of disorientation and performance impairment that happens after awakening. Estimates of the duration of sleep inertia vary substantially, ranging from 1 min to 4 h.[48] Generally, sleep inertia seems to be worse when the individual is awoken during deep, slow-wave sleep, and after previous sleep loss.

Legal implications of 24-h operations

Accidents associated with sleepiness can lead to legal proceedings, for example, charges of culpable driving. In a recent case in the USA, the family of a woman killed in a road accident after a tractor-trailer hit the back of her vehicle received a US$24 million settlement from the driver's employer. The plaintiffs alleged that the employer's violation of hours of work regulations resulted in driver fatigue, which caused the collision.[49]

According to common law principles, actions done while sleeping will be construed as involuntary and hence would not give rise to criminal liability, so long as the offence is not one of negligence or strict liability. There is, however, likely to be a period of time immediately before sleep onset when the individual is aware of the fact that his or her driving is potentially dangerous due to high levels of sleepiness. Horne and Reyner[10] note that although most drivers do not recall having fallen asleep, they are highly likely to have been aware of the precursory feelings of sleepiness. Such data have important implications for questions of culpability in sleepiness-related accidents.

Accidents that seem to be caused by sleepiness might also give rise to negligence claims. In acting while extremely sleepy, a duty of care might be breached, and this breach could be deemed to have caused damage to the plaintiff. Special liability regimes have been established to cover employers' liability. Indeed, workplace accidents are known to result in more tort claims than any other category of accidents, except road accidents. In UK law, the employer has a duty to ensure ". . . as far as is reasonably practicable, that employees and non-employees are not exposed to risks to their health or safety".[50] In legal systems throughout the world, corporations, rather than individuals, are being recognised as the subject of criminal and civil proceedings, including manslaughter.

In addition to the adverse consequences of sleepiness, the reported increase in risk of cardiovascular disease and other health problems in shiftworkers suggests that litigation will increase over time. The burden on employers to take reasonable steps to ensure that risks to health and safety are prevented or kept to a minimum is likely to increase. Practical strategies to improve tolerance to shiftwork and transmeridian travel are recommended, such as seeking advice from chronobiologists for improved design of shiftwork and air travel schedules, exposure to bright light to hasten circadian adaptation and sustain alertness and performance during night work, access to caffeinated beverages, provision of regular rest breaks and napping facilities, education programmes on effective methods of managing sleepiness and other consequences of shiftwork. Implementation of technologies to manage fatigue[51] could be justified in situations in which risk to public and environmental safety, health, and productivity is substantial.

Statutory provisions, such as the Working Time Regulations 1998 in the UK, are now in place to control hours of work. One notable shortfall with present regulations is that circadian effects on mental alertness and performance are not adequately recognised.[10] In view of the increased risk of accidents during early hours of the morning, greater regulation of work practices during these times is warranted.

Sleep deprivation can have effects on mental alertness that are similar in magnitude to those seen in people with alcohol concentrations widely regarded to be unsafe (figure 4). In the same way that use of alcohol while driving and during work hours has been legislated, it is foreseeable that similar rules will be developed for sleep deprivation.

Conclusions

Enormous progress has been made in our understanding of circadian rhythms and our ability to manipulate them. Endogenous periodicity is an inherited characteristic for which several candidate genes have been identified. Human tolerance to shiftwork and transmeridian travel

could be associated with endogenous periodicity, and thus, changing the design of shift schedules, and giving specific advice to individual workers could help to improve their health and reduce risk factors for major disease.

Biological time is not only scientifically important, but it also greatly affects the productivity and health of a nation. The cost to the nation's health of working out of phase with our biological clocks is probably incalculable at present. In the short term, poor sleep, gastrointestinal problems, higher accident rate, and social problems are evident. Employers and individuals need to be aware of the major performance and alertness decrements associated with night activity and how to best manage and counteract them. It is worth noting that in a classic early experiment, forcing flies constantly to shift their clocks led to substantially lowered life expectancy. The same result was recorded in cardiomyopathic hamsters that had their light-dark cycle shifted on a weekly basis.[53] Manipulation of human beings in the same way would, of course, be unethical. However, either by choice or by necessity, many of us are doing an uncontrolled experiment on ourselves.

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The uses of error: diagnostic preferences

A 54-year-old man was admitted to the nephrology unit with acute renal failure. He had a one week history of cough, fever, arthralgia, and back pain, and had not passed urine for the past 12 hours. He had α-1-antitrypsin deficiency emphysema with recurrent pulmonary infections since the age of 40. He was peripherally cyanosed and had biochemical renal failure, hyperkalemia, respiratory acidosis. and an elevated erythrocyte sedimentation rate. Chest radiography showed consolidation at the right pulmonary base. Urinalysis showed 1+ proteinuria and 10-20 erythrocytes per high power field.

He was put on dialysis, and large-spectrum antibiotics were administered, but he did not improve. The next day he developed cough and hemoptysis; chest radiographs showed enlarging consolidation. A renal ultrasound excluded urinary tract obstruction. Serum anti-nuclear antibodies, anti-DNA antibodies, and antineutrophilic cytoplasmic antibodies were negative. The patient had normal complement levels. Nevertheless, we still considered systemic vasculitis a likely diagnosis, since these tests may be falsely negative. A renal biopsy was performed.

Histology showed extensive renal cortical necrosis. Glomeruli had severe ischemic damage but no signs of inflammation. Doppler ultrasonography showed the bilateral absence of renal blood flow. Aortography showed dissection of the thoracic aorta below the emergence of the left subclavian artery. The dissection extended to both renal arteries, but spared the coeliac tripod. The right lung consolidation enlarged, and a broncho-alveolar lavage yielded *Candida albicans*. Anti-fungals were administered but the patient died of septic shock. An autopsy was not performed due to the family's opposition.

The clinical presentation of acute nephritic syndrome combined with pulmonary hemorrhage, (hemoptysis or pulmonary infiltrates) is characteristic of systemic vasculitis (particularly Wegener's granulomatosis), lupus, and Goodpasture's syndrome. Although neither sensitive or specific, common complaints and signs of vasculitis include fatigue, weakness, fever, arthralgia, abdominal pain, hypertension, and renal insufficiency. The present case had all these features.

We perform an average 150-170 renal biopsies a year, and have performed 3 000 renal biopsies over a period of 25 years with very few complications. We have a high standard of renal pathologists, and extensive clinical experience and research interest in glomerular diseases. Therefore, when the diagnosis in patient is not rapidly apparent, we tend to perform a renal biopsy, provided that there are no contraindications. In this case the renal biopsy showed that the cause was not an inflammatory disease, but that acute renal failure was ischemic in nature, due to complete occlusion of renal arteries. However, renal biopsy is a rather unsatisfactory approach to such a diagnosis, and, more importantly, a dangerous manoeuvre in a patient with uremia, respiratory insufficiency, and severe hypertension.

When the case was reviewed we recognized that the urine sediment was not consistent with an inflammatory disease, and anuria is very unusual in acute nephritic syndromes. The lung involvement was not typical of a renal pulmonary syndrome and the negative results of laboratory tests should have been given more weight. On the other hand, symptoms of acute aortic dissection were almost nonexistent. The patient had not complained of abrupt and severe thoracic pain, which occurs in 90%. Acute renal ischemia is present in 13% of patients at presentation. but if one considers that the reported incidence of acute aortic dissection is 27 per million people, this is a rare presentation. We learned from this case that proficiency in one area of medicine, or vast experience with a particular diagnostic manoeuvre may lead one to overestimate signs and symptoms that could be interpreted otherwise, resulting in a completely different diagnosis.

Arrigo Schieppati, Giuseppe Remuzzi
Negri Bergamo Laboratories, 24125 Bergamo, Itaty