Occupational Medicine 2010;**60:**10–20
doi:10.1093/occmed/kqp162

IN-DEPTH REVIEW

Shift work: coping with the biological clock

Josephine Arendt

Abstract The internal circadian clock adapts slowly, if at all, to rapid transitions between different shift schedules. This leads to misalignment (desynchrony) of rhythmic physiological systems, such as sleep, alertness, performance, metabolism and the hormones melatonin and cortisol, with the imposed work–rest schedule. Consequences include sleep deprivation and poor performance. Clock gene variants may influence tolerance of sleep deprivation. Shift work is associated with an increased risk of major disease (heart disease and cancer) and this may also, at least in part, be attributed to frequent circadian desynchrony. Abnormal metabolism has been invoked as a contributory factor to the increased risk of heart disease. There is recent evidence for an increased risk of certain cancers, with hypothesized causal roles of light at night, melatonin suppression and circadian desynchrony. Various strategies exist for coping with circadian desynchrony and for hastening circadian realignment (if desired). The most important factor in manipulating the circadian system is exposure to and/or avoidance of bright light at specific times of the 'biological night'.

Key words Body clock; cancer; circadian rhythm; heart disease; light; melatonin; metabolism; shift work.

Introduction

Many reviews have been published regarding the subjective perceptions, health, performance and psychosocial aspects of shift work [1–11]. There is little doubt that shift work is associated with a number of health problems, for example poor sleep, gastrointestinal disorders, abnormal metabolic responses and increased risk of accidents. A longer term risk of major disease such as heart disease and cancer is beginning to be appreciated. This review will concentrate on shift work in relation to biological rhythms since disturbed rhythms appear to underlie many of the short- and long-term health problems of shift workers [12–14]. To this end, an introduction to the subject is provided.

Literature search

A literature search with the keywords 'shift work' and 'circadian' gave 1034 references in PubMed. Since the pineal hormone melatonin is currently used as the primary output marker of the internal clock (as well as its actions as a chronobiotic), the search was then restricted to ((shift work) and (circadian) and (melatonin)). This provided 189 references, which together with the author's personal collection formed the basis of this review.

Centre for Chronobiology, Faculty of Health and Medical Sciences, University of Surrey, Guildford, Surrey GU2 7XH, UK.

Correspondence to: Josephine Arendt, Centre for Chronobiology, Faculty of Health and Medical Sciences, University of Surrey, Guildford, Surrey GU2 7XH, UK. Tel: 01482 689712; fax: 01483 689712; e-mail: arendtjo@aol.com

Importance of biological rhythms to health

Biological rhythms serve to align our physiological functions with the environment. We are a diurnal species and thus, we normally sleep at night and are active during the daytime. The timing of functions with prominent rhythms such as sleep, sleepiness, metabolism, alertness and performance in a normal environment is such that they are optimal during the most suitable phase of the day (Figure 1). Abrupt deviations from 'normal' timing of work and sleep can lead to problems, for example sleep taken during the day is usually shorter and of worse quality than when taken at night [6,15]. Alertness and performance reach their nadir at night during peak sleep propensity and fatigue [13,16,17] and close to the low point of core body temperature and the peak of melatonin secretion. The health problems and increased risk of major disease in long-term shift workers are ascribed largely to working out of phase with the internal biological clock. It is likely that many perceptions of the detrimental effects of clock disruption or abnormal timing derive from observations in shift workers.

Characteristics of circadian rhythms

Basic properties

Everything is rhythmic unless proved otherwise [18]. Biological rhythms of various periodicity are ubiquitous. The frequency displayed varies from fractions of a second (for example the firing of neurones) to years (for example

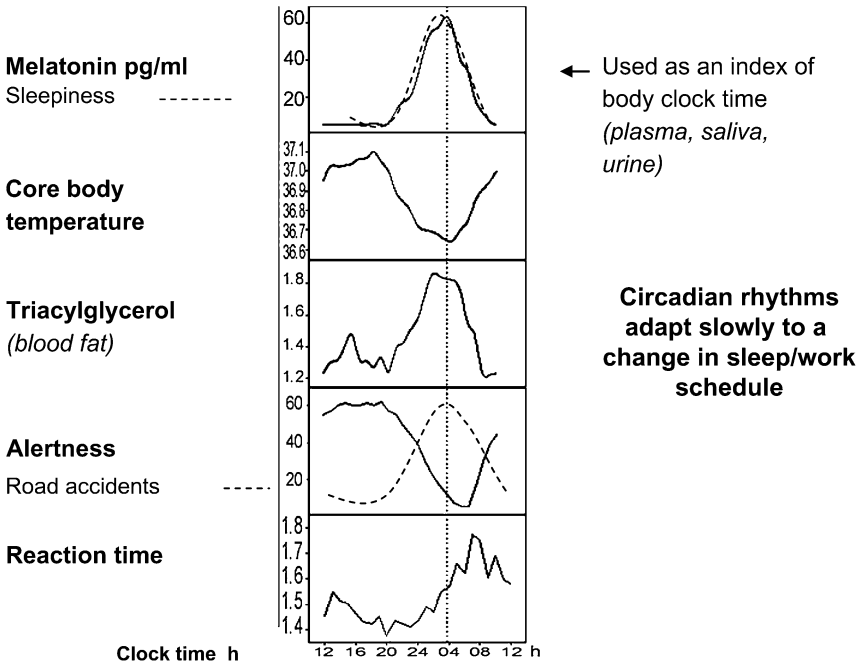

Figure 1. Diagrammatic examples of circadian rhythms, from Rajaratnam and Arendt, *Lancet* 2001 [13], by permission.

population variations). By far, the most information is available concerning daily rhythms [18,19]. They are either externally imposed, internally generated or more frequently a combination of these two factors. Internally generated rhythms with approximately a 24 h period are known as circadian, from the Latin 'circa diem', 'about a day'). Circadian rhythms serve to temporally programme the daily sequence of metabolic and behavioural changes. By definition, they persist in the absence of time cues such as alternating light and darkness and are coordinated by an internal biological clock (pacemaker, oscillator) situated in the suprachiasmatic nuclei (SCN) of the brain hypothalamus [20]. The basis of circadian rhythm generation is a negative feedback loop of clock gene expression [21,22].

Individuals kept in a time-free environment (or at least with very weak time cues) manifest their own endogenous periodicity referred to as 'free-running'. The free-running period is individually variable and is an inherited characteristic. On average, the human endogenous period (or tau) is about 24.2–3 h although this does depend on previous experience of time cues [18,23]. Synchronization or entrainment of the circadian clock to 24 h is dependent on suitable time cues, also known as 'zeitgebers'. In circadian literature, synchronization means that rhythms display a 24 h period but may not necessarily be in the right phase, for example, abnormally delayed or advanced. Entrainment means that the rhythms are synchronized with the appropriate phase. When entrained to the 24 h day, a short endogenous tau is associated with morning diurnal preference (larks) and a long tau with evening preference (owls) [18].

Circadian response to time cues

Because the circadian clock period is not exactly 24 h, it must be reset regularly (phase shifted) to maintain a 24 h period. The most important time cue for maintaining a 24 h period is the light dark cycle acting partly via a novel retinal photoreceptor system and a novel photopigment melanopsin (circadian photoreception) [24]. Recent evidence indicates that short wavelengths of light (460–480 nm, blue) have the most powerful resetting effects [25]. Blind people with no conscious or unconscious light perception frequently display free-running rhythms, underlining the importance of light. The timing of sleep also has an influence together with minor 'non-photic' zeitgebers such as exercise, social cues, clock time and food ingestion. Specific manipulation of food timing in animals influences a so-called food entrainable oscillator, which is independent of the SCN [26]. The content of meals in humans may also have a minor influence.

The circadian response (change in timing or phase shift) to light exposure, and indeed to other time cues, is dependent on the strength and timing of the stimulus. It can be described by a 'phase response' curve (Figure 2) [27,28]. The central clock adapts slowly, and with considerable individual variability, to a rapid shift in work time or time zone. After a time zone change, the average rate often approximates to 1 h of adaptive shift per day. After an abrupt shift in work time, the change is very variable as discussed later [29–31]. During the process of adaptation, endogenous rhythms are out of phase with the external environment (external desynchronization). They may also be out phase with each other, i.e. assume a transitory

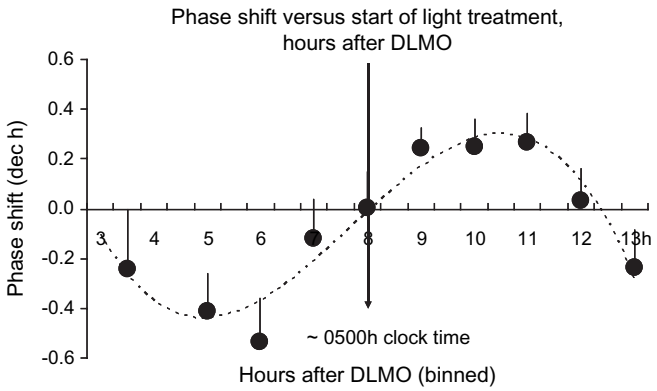

Figure 2. Circadian response ('phase response curve', shift of the melatonin rhythm, advances are positive, delays are negative) to a 1–2 h light pulse, ca 300 lux, 500 nm, at different times of night. DLMO = dim light melatonin onset, on average at ~2100 h, thus 8 h after DLMO = 0500 h clock time. From Paul *et al.* [28], by permission.

abnormal phase relationship (internal desynchronization). This condition is often referred to as 'circadian desynchrony'. Time cues or zeitgebers are all important in controlling the circadian response to such changes. In general, it is easier to delay the clock than to advance it in view of the >24 h period of most people. During a period of desynchrony, for example, a single night of night shift in a sequence of days, workers are attempting to sleep at a time of maximum alertness and to work at the nadir of alertness and performance. If adaptation of the clock to a new work schedule occurs, the problems of desynchrony resolve [32–35].

Genetic basis of circadian rhythms

Many of the genes concerned with circadian rhythm generation in mammals and other species have now been identified, e.g. *CLOCK, PER1, PER2, PER3, TIM, CRY1, CRY2, BMAL1, REV-ERBALPHA*. The mechanism is similar in all species investigated and substantial homology exists between, for example, *Drosophila* and mammals. Oscillation of clock genes also occurs in peripheral structures, and in general, they are considered to be coordinated through SCN activity. However, it is possible to shift the timing of some peripheral oscillations (for example, in the liver by timed feeding), independently of the SCN [36]. Investigation of polymorphisms in human clock genes in relation to occupational health and disease is in its infancy. Some polymorphisms have been identified and associations are emerging with phenotypic characteristics such as diurnal preference (larks–owls), intrinsic period, vulnerability to disease and response to sleep deprivation [37–39].

The circadian clock influences hormones, behaviour, cognitive function, metabolism, cell proliferation, apoptosis and responses to genotoxic stress [22]. There is new strong evidence concerning the importance of circadian control for health in that disruption of circadian clock gene expression can lead to increased incidence or progression of cancer (in animals) [22,40].

Examples of rhythms relevant to human disease

Some examples of human rhythms in disease processes include night time asthma, early morning increases in blood pressure, death rate from cardiovascular disease and stroke, disrupted menstrual cycles, abnormal cortisol rhythm in Cushing's syndrome, sleep disorders for example delayed sleep phase syndrome, advanced sleep phase syndrome, non-24 h sleep wake cycles (especially in the blind), some psychiatric disorders. Numerous aspects of human biochemistry show rhythmicity, even urinary creatinine. Thus diagnostic tests should be aware of these rhythms. Measurement of a given rhythmic variable in someone who has just crossed several time zones, or worked a series of night shifts, can give false-negative or false-positive results. Moreover, many drugs have a rhythmic variation in both pharmacokinetics and efficacy (chronopharmacology).

The melatonin rhythm

A darkness hormone

Melatonin (*N*-acetyl-5-methoxytryptamine) in an indolic hormone whose principal physiological function is to provide a humoral time cue for the organization of seasonal and circadian rhythms [41]. The pineal gland secretes melatonin with a marked circadian rhythm, peaking at night—it has been called the 'darkness hormone' and the duration of its secretion is directly related to the length of the night. In animals which depend on day length to time their seasonal physiology, the length of melatonin secretion signals the length of the night. In humans, its circulating concentrations are high from ~2100 to 0700 h with large individual variations. This period can be used to define 'biological night'. The peak secretion occurs ~0400 h, closely associated with the nadir of core body temperature, alertness and performance (Figure 1). In specific circumstances, humans may also show changes in the duration of secretion [41].

Melatonin as a chronobiotic

Melatonin is not only a so-called 'hand of the clock', it has the ability to induce sleepiness or sleep, change circadian phase and to entrain free-running rhythms when administered in suitable doses and timing [42]. There are several phase response curves to melatonin with slight differences, which can be used to predict the chosen timing in order to hasten a circadian phase shift. This is important in a shift work context given that a number of

attempts have been made to treat shift workers with melatonin with variable results.

Melatonin suppression by light

Light of sufficient intensity and spectral composition will suppress melatonin production at night [41,43]. Suppression is detectable at 30–50 lux and maximum from around 1000–2000 lux. Natural daylight can attain >100 000 lux. This suppression is associated with rapidly increased alertness and core body temperature, although causal relationships are not clear. It is important in a shift work context as light suppression of melatonin has been hypothesized to be detrimental to health [44]. A night shift worker whose circadian clock is in day mode, or unadapted, will secrete melatonin during work hours. Similarly, a worker who has adapted their clock to night shift will secrete melatonin during the day and on return to day shift or rest days will secrete melatonin during the hours of natural daylight. Actual personal light exposure during night shift work has rarely been measured, examples of personal light exposure on North Sea oil rigs are shown in [45]. In general, the amount of suppression reported during field studies on night shift is minor, ~20% [46,47].

Melatonin indicates the timing of the biological clock

Shifts in the timing of melatonin are considered to represent changes in timing of the central clock. Measurement of melatonin in plasma, saliva or its urinary metabolite 6-sulphatoxymelatonin [43] provides the best peripheral measure of central clock timing (Figure 3). Other marker rhythms such as core body temperature and cortisol are more subject to so-called masking, whereby an internal or external influence distorts the rhythm. For example, exercise and food strongly influence core temperature and stress modifies the cortisol rhythm. The most reliable results regarding circadian status in shift work have been obtained with melatonin measures and this review will concentrate on melatonin-derived information.

Circadian desynchrony in shift work

Relationship to work hours

There are many varieties of shift work and a legal definition does not appear to exist except for 'working outside normal working hours'. For the purposes of this review, let us consider that it is working during 'average' biological night, i.e. 2100–0700 h. Also for the purposes of this review, the assumption is made, based on controlled laboratory experiments, that when sleep is taken during the period of peak melatonin secretion (and thus, in theory, the nadir of alertness, performance and core body temperature), it is optimized. In night shift conditions, if peak melatonin secretion is shifted to occur during day sleep, it is presumed that adaptation to night shift has occurred.

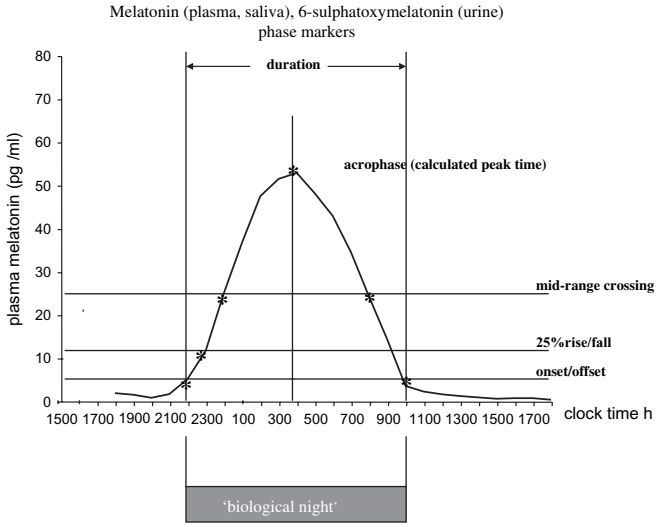

Figure 3. Characteristics of the melatonin rhythm used to define timing of the internal clock. From [43] by permission.

The most numerically important shift work conditions, at least in the UK, are irregular night shifts (sometimes nights and sometimes days) and rotating schedules (information from the Office of National Statistics) (Box 1).

Examples of rotations include 3 days early shift (e.g. 0600–1400 h), 3 days late shift (e.g. 1400–2200 h), 3 days night shift (e.g. 2200–0600 h) and rest days. These common schedules do not allow the internal clock to adapt fully to night shift since there is substantial inertia in the circadian system. After abrupt large changes in time cues, the daily shifts in circadian timing rarely exceed 1–1.5 h on average without interventions. Exposure to morning light (in the travel home window after night shift) is at a time that opposes a delay shift of the clock to adapt (Figure 2), and daytime social cues counter circadian adaptation. Data from field studies indicate that the greater the morning light exposure the less circadian adaptation is seen [48]. In temperate latitudes natural bright light will be more prevalent in summer in the early morning, and any shift of the circadian system during night shift will in theory be countered more strongly than in winter.

Partial shifts in circadian timing can be seen in short-term night shift work, and a relationship to the timing of light exposure is present, either delays or advances, in relation to the light phase response curve [29,49,50]. Natural light exposure, the most powerful influence, evidently depends on the shift timing. Also important is the diurnal preference of the subjects [29]. Evening preference people are reported, as might be expected, to have a greater tendency to delay and morning people to advance [29,47].

Most permanent or long-term night shift workers (with exceptions, see below) do not adapt their circadian system

Box 1. Types of shift work

UK Labour Force Surveys, Office for National Statistics, April to June, 2005
All shift workers, 3 083 270, 11% of working population (28 301 000)
Rotating shifts, 1 260 845
Permanent nightshifts, 290 661
Sometimes nights, sometimes days, 416 412
Weekend shifts, 49 407
Other types of shift work, 1 065 945

Table 1. Examples of shorter sleep in night shift workers

4.8 h, night shift, fast rotation, Axelsson *et al.* [52]
5–6 h, morning shift starting before 6 am, Kecklund and Akerstedt [53]
6.04 h, 7 nights, 7 days, 12 h on 12 h off, Gibbs *et al.* [45]
5.83 h, 4 h on 8 h off, permanent night watch, ships crew, Arendt *et al.* [54]
Compare
7 h (approximately) healthy adults, Groeger *et al.* [55]
8.7 h healthy young men, sleep *ad lib*, Rajaratnam *et al.* [56]

to the imposed work schedule. A recent meta-analysis of 6-sulphatoxymelatonin rhythms in permanent night workers indicates that only a small percentage (<3%) shows complete circadian adaptation and <25% adjust to the point that some benefit would be derived from the adaptive shift [51]. This may depend on the ability to maintain night activity and day sleep on days off as well as other factors such as diurnal preference. However, there is a paucity of data and further research is needed.

Thus, the vast majority of shift workers will be working during their circadian nadir and trying to sleep during periods of maximum alertness. The curtailment of sleep when taken during the day in shift workers is well documented and is a cause of sleep deprivation. Some examples of short sleep are shown in Table 1.

Sleep deprivation

Sleep deprivation concomitant (*inter alia*) upon circadian desynchrony has been attributed a causal role in obesity, metabolic syndrome, glucose intolerance/diabetes, increased accidents and errors. Sleep restriction has also been associated with alterations of neuroendocrine control of appetite [57–60].

In relation to sleep deprivation, an important study of interns weekly work hours in the USA found that they made 36% more serious medical errors during a traditional work schedule than during an intervention schedule that eliminated extended work shifts. These included 21% more serious medication errors and 5.6 times as many serious diagnostic errors [60].

Changing from day to night shift often implies a period of 20–24 h without sleep. The decrements in performance during the latter part of this sleep deprivation may be equivalent to an illegal level of alcohol in the blood [16]. Accidents following a combination of sleep deprivation and working during the circadian nadir in performance and the maximum sleep propensity have led to litigation against individuals and employers [13]. It is considered that fatigue may be a more important cause of transport accidents than alcohol (Figure 4).

Metabolism

The circadian system regulates metabolism [61] and increasing evidence relates circadian desynchrony to disorders such as metabolic syndrome (insulin resistance, high blood pressure, central obesity, decreased high density lipoprotein (HDL) cholesterol, elevated triglycerides (triacylglycerol, TAG) and cardiovascular disease [59]. For example, eating a standard meal at night (biological night) leads to high blood lipid (TAG) and evidence for insulin resistance, compared to the same meal taken during the day [62,63]. Interestingly, there is some evidence that men are more susceptible to these metabolic abnormalities than women. TAG is an independent risk factor for development of heart disease. This may provide at least a partial explanation for the increased risk of heart disease in shift workers. In large surveys, shift workers have higher TAG levels as well as higher total cholesterol than the general population [11,64].

There are associations between polymorphisms in the gene *CLOCK*, obesity and the metabolic syndrome in man, and mice bearing a particular mutation of the gene *CLOCK* develop metabolic syndrome and obesity [65,66].

Circadian adaptation in unusual environments

Some exceptions to the general rule that shift workers do not fully adapt to night shift are found in isolated environments. On the British Antarctic Base of Halley, 75°S, each base member does a week of night shift (2000–0800 h, fire watch) at a time, in rotation with other personnel. The vast majority of people shift their circadian system, assessed by aMT6s rhythms in urine, by up to 10–12 h to align with the new work schedule, within a week [67,68]. Thus, the peak of melatonin production occurs within the daytime sleep period—an important condition for sleep duration, latency and quality. This is thought to be due to the lack of social and family obligations, no requirement to return home in natural light and in winter when the sun does not rise for 3 months, a lack of conflicting light exposure. In these circumstances, it is apparent that owls adapt by delay faster than larks [69]. Problems occur when endeavouring to adapt back to day work particularly in winter. Realignment of the circadian system can take weeks and some people will free-run for a time.

These observations in Antarctica prompted studies in somewhat similar circumstances on North Sea oil rigs.

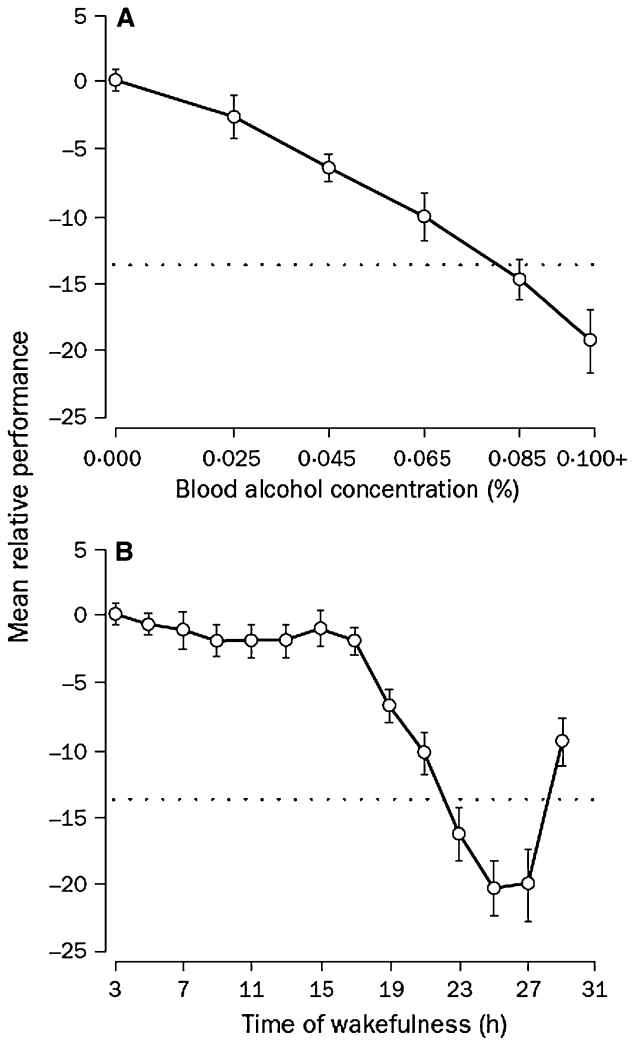

Figure 4. Comparison of the effect of blood alcohol concentration (BAC) and hours of wakefulness on task performance. Higher scores indicate better performance. The decrement in mean performance at blood alcohol concentrations of 0.10% or greater is similar in magnitude to those observed after 25–27 h of wakefulness. From Rajaratnam and Arendt [13] after Dawson and Reid [16] by permission. (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). (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).

Work schedules vary but tours of duty usually last for 2–3 weeks in a socially isolated environment at high latitudes. Here, working 1800–0600 h for ≥1 weeks also leads to full circadian adaptation in the majority of cases with the accompanying problems returning to day life [30,70,71]. Interestingly, a 1900–0700 h schedule is less conducive to circadian adaptation, possibly due to early morning light exposure after work especially in summer [72]. Sleep is worse during this shift than the 1800–0600 h shift. The so-called 'swing shifts' worked in the North Sea present a confused picture. Seven night shifts (1800–0600 h) followed by 7 day shifts (0600–1800 h) leads in most people to adaptation to nights but with a very mixed response to the following days [30,73] (Figure 5). Some people delay, some advance and many show little readaptation to days during the first week. The response is partly predictable from the initial circadian phase position: delayed, intermediate or advanced. Other schedules such as a 7 day, 1200–2400 h day shift followed by a 7 day 2400–1200 h night shift show partial or no adaptation to night shift which is dependent on season [71]. Again, this can be attributed to light exposure countering adaptation.

Such circumstances, when workers show different circadian timings according to whether or not they have adapted to nights, have allowed field assessments of the metabolic consequences of a night shift meal. As with controlled laboratory experiments, elevated TAG, low density lipoprotein (LDL) cholesterol and evidence of insulin resistance were found when unadapted [45]. These sequelae resolved when adaptation had occurred.

Marine watchkeeping

Special cases of shift working are seen in marine watchkeeping systems. There are very few data relating to melatonin rhythms; however, a study in submarines has shown evidence that crew can free run while working an 18 h day, submerged for long periods [74]. Circadian adaptation was studied in crew working 4 h on and 8 h off on fixed or rotating schedules on a British Antarctic Survey ship travelling from the UK to 75°S. They showed evidence of partial circadian adaptation to the 1200–1600 h, 2400–0400 h fixed watch but not to weekly rotating watches [54].

Light at night and the risk of major disease

It is not the purpose of this review to evaluate the epidemiological evidence for increased risk of disease in shift work; this can be found elsewhere. It is generally accepted that there is an increased risk of heart disease and some contributory factors related to the biological clock have been discussed above.

A possible significant association was identified between female breast cancer and shift work some time ago [75]. This is potentially a major problem since estimates from the Spring 2002 wave of the Labour Force survey suggest that an estimated 1.8 million women in Great Britain usually or sometimes do shift work. Of these, an estimated 400 000 are involved in night work of various schedules [76]. In 2006, the World Health Organization (WHO) (International Agency for Research on Cancer, IARC) published a brief report in the *Lancet* of an expert meeting on whether or not shift work was associated with an increased risk of cancer, particularly breast cancer. The conclusion was that shift work was a probable carcinogen [77]. A full

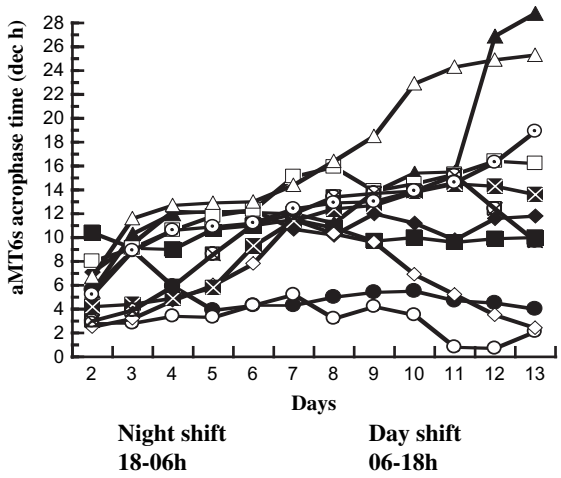

Figure 5. Progression of the individual timing of the melatonin rhythm (by urinary aMT6s), during a week of nights (1800–0600 h) followed by a week of days (0600–1800 h) in 11 individuals working on a North Sea oil rig. Most shift their timing such that at the end of nights the peak of melatonin is during the daytime sleep and thus, they are adapted. The subsequent response to a change to day work is highly variable. From [30] by permission.

monograph is expected from this meeting but has not yet been published. There are considerable implications arising from this decision and, for example, according to the UK national press in March 2009, the Danish government decided to compensate shift workers who develop breast cancer. Both the UK and Dutch governments also issued publications discussing the evidence and in general decided that further epidemiological evidence and mechanistic data were needed [78,79]. Assuming that the risk assessments are correct, let us consider the possible mechanisms.

The most well-known theory concerning cancer and shift work relates to light exposure at night (light at night, LAN). Stevens and Davis [44] hypothesized that the increasing incidence of breast cancer in the developed world was due to light exposure at night. He further proposed that, since light suppresses melatonin and melatonin has some oncostatic activity in animals, the increase in breast cancer was due to a decrease in melatonin. Numerous questions arise from this proposal, some of which can be addressed. The WHO (IARC) expert meeting concluded that there was definite evidence for anti-cancer effects of melatonin in animals and *in vitro* but little in humans. It should be noted that human *in vivo* data are sparse. The data which directly addressed the cause and effect relationship between melatonin and human breast cancer involved maintaining human breast transplants (xenografts) in rats and assessing short-term markers of cancer with and without circulating endogenous levels of melatonin. Physiological levels of melatonin were able to reduce or abolish carcinogenic changes in these markers [80]. This latter study does suggest that endogenous melatonin has anti-proliferative effects working via a membrane receptor. However, not all studies have shown anti-proliferative effects of melatonin *in vitro*. Is melatonin suppressed in night shift workers? Again the data are sparse, the existing evidence mentioned previously suggests that an ~20% reduction may be found during the night shift. Is a 20% reduction in melatonin carcinogenic? There is no answer to this question. However, it should be noted that adrenergic beta-receptor blocking drugs such as atenolol and propanolol suppress melatonin and are not known to be carcinogenic [41]. Moreover, the individual variability in melatonin production is very large indeed and in cross-sectional studies, large numbers of subjects are needed to show this small overall reduction [41].

More convincing are the effects of general circadian disruption in animals [81]. Exposure of animals to continuous light increases vulnerability to cancer development [82,83]. Subjecting rodents to forced phase shifts analogous to rotating shift work or frequent time zone change substantially increases proliferation of implanted cancers [40]. Manipulation of clock gene function likewise has carcinogenic effects [14,22,84,85] and the circadian clock is considered to be a tumour suppressor. So the case is close to being made for circadian disruption leading to cancer.

The problem is that increasing light at night in short-term shift work leads to improved alertness, performance and possibly metabolism, while no doubt increasing melatonin suppression. At present, investigations are proceeding on the use of glasses, which can block the short wavelengths most likely to suppress melatonin while hopefully maintaining alertness and performance.

Approaches to reducing desynchrony

The question arises as to the benefits and disadvantages of aiding or countering adaptation in order to secure the maximum duration of good quality sleep and other health benefits. In the unusual case of full adaptation, it makes sense to hasten this process and that of readaptation to day work. In short-term night shift, it may be more useful to maintain daytime circadian phase while using strategies such as alerting stimulants (caffeine and possibly modafinil), quiet dark sleeping quarters (and possibly hypnotics) to preserve sleep and performance.

Light of suitable spectral composition and intensity can be used to adjust the timing and probably amplitude of circadian rhythms. The hormone melatonin can also act as a zeitgeber (*vide supra*). Light treatment during the first half of biological night prior to the melatonin peak will delay circadian rhythms and during the latter half, after the melatonin peak, will advance rhythms (Figure 2). Melatonin treatment by contrast advances rhythms in the first half of biological night and delays them in the latter half.

There is no doubt that in controlled laboratory situations, and with good compliance at home, both light and

melatonin, separately or in combination, can be used with correct timing to hasten phase shift of the circadian system to align it with the new work–rest schedule [32,43,50,86]. There are clear benefits for sleep, alertness and performance. Moreover with suitable timing, the sleep-inducing effects of melatonin during 'biological day' can also be exploited. In field situations, the results are inconsistent. Very probably this is due to the large individual differences in response to phase shift and in consequence mistiming of the treatment. However, in studies offshore and in Antarctica, useful results have been reported with timed light treatment [67,87]. The author is only aware of one combined treatment study, which was offshore and with beneficial effects [88]. It is possible that the most useful application of melatonin to shift workers would be to facilitate sleep or a nap, prior to night shift. It is particularly difficult to sleep in the early evening, and the combination of low-dose melatonin, a dark room and recumbency is very effective at enabling sleep at this time of day [56].

An alternative approach has been described recently. This is to shift the circadian system, using timed light and melatonin, just to the point where the melatonin peak falls within the sleep period, avoiding large shifts which lead to readaptation problems [34,89]. This strategy appears to provide benefit for sleep, alertness and performance. However, if the timing is wrong, the opposite of the desired result will be produced. For example, instead of adapting to an 8 h advance in work time by advancing the clock, the system may delay. Avoidance of light at the wrong time is possibly more important than the light treatment itself.

A genetic variant predicting intolerance to sleep deprivation

Morningness has been related to intolerance to shift work in some studies although not all are consistent. Recently, a length polymorphism in the clock gene *PER3* (*PER3* 5/5, 4/5, 4/4) was found to relate to diurnal preference, 5/5 being associated with extreme morningness and 4/4 with extreme eveningness [38]. Subsequently, it was found that the 5/5 genotype suffered more from sleep deprivation than the 4/4 genotype and these differences could be explained by an effect of the polymorphism on sleep homeostasis [37]: it was associated with greater sleep propensity and a higher proportion of slow-wave sleep than the 4/4 genotype. Most importantly, the subjects with the 5/5 variant suffered far greater consequences of sleep deprivation in terms of performance (notably during the circadian nadir) than the 4/4 genotypes. Mongrain *et al.* [90] have also shown that morning types have a higher homeostatic response to sleep disruption than evening types. This observation suggests that workers who are extreme morning types should choose their schedules carefully with regard to preserving sleep. One further study addressing a similar question, but different methodology, found an association with sleep homeostasis but did not confirm the effect on neurobehavioural responses [91].

It is of interest to note there are also preliminary reports of greater susceptibility to breast cancer in women with the 5/5 variant and prostate cancer in men with the *CRY2*-variant C allele [39,92]. No doubt more information will be available shortly given the importance of predicting the possible health consequences of shift work.

Acknowledgements

I would like to thank all colleagues, students, volunteers and funding bodies who have provided input, samples and support for our work on biological rhythms over the years. I would particularly like to mention Mark Midwinter, Jonathan Ross, Jon Lund, Lil Ng, Gavin Francis, Victoria Mottram (Antarctic Base doctors), Richard Barnes, Michelle Gibbs and Helen Thorne (University of Surrey PhD students) who persuaded numerous workers at Halley Base (75°S) and on the North Sea oil installations to provide sequential urine samples during their period offshore. These heroic efforts have provided a dynamic picture of the long-term circadian response to phase shift.

Conflicts of interest

None declared.

References

1. Akerstedt T. Psychological and psychophysiological effects of shift work. *Scand J Work Environ Health* 1990; **16(Suppl. 1):**67–73.
2. Knutsson A. Health disorders of shift workers. *Occup Med (Lond)* 2003;**53:**103–108.
3. Nicholson PJ, D'Auria DA. Shift work, health, the working time regulations and health assessments. *Occup Med (Lond)* 1999;**49:**127–137.
4. Tucker P, Knowles SR. Review of studies that have used the Standard Shiftwork Index: evidence for the underlying model of shiftwork and health. *Appl Ergon* 2008;**39:**550–564.
5. Knauth P. Changing schedules: shiftwork. *Chronobiol Int* 1997;**14:**159–171.
6. Akerstedt T. Shift work and sleep disorders. *Sleep* 2005;**28:**9–11.
7. Akerstedt T, Kecklund G, Johansson SE. Shift work and mortality. *Chronobiol Int* 2004;**21:**1055–1061.
8. Folkard S, Tucker P. Shift work, safety and productivity. *Occup Med (Lond)* 2003;**53:**95–101.
9. Karlsson B, Knutsson A, Lindahl B. Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27,485 people. *Occup Environ Med* 2001;**58:**747–752.
10. Megdal SP, Kroenke CH, Laden F, Pukkala E, Schernhammer ES. Night work and breast cancer risk: a systematic review and meta-analysis. *Eur J Cancer* 2005;**41:** 2023–2032.

11. Knutsson A, Boggild H. Shiftwork and cardiovascular disease: review of disease mechanisms. *Rev Environ Health* 2000;**15:**359–372.
12. Moore-Ede MC, Richardson GS. Medical implications of shift-work. *Annu Rev Med* 1985;**36:**607–617.
13. Rajaratnam SM, Arendt J. Health in a 24-h society. *Lancet* 2001;**358:**999–1005.
14. Stevens RG. Circadian disruption and breast cancer: from melatonin to clock genes. *Epidemiology* 2005;**16:**254–258.
15. Akerstedt T, Ingre M, Broman JE, Kecklund G. Disturbed sleep in shift workers, day workers, and insomniacs. *Chronobiol Int* 2008;**25:**333–348.
16. Dawson D, Reid K. Fatigue, alcohol and performance impairment. *Nature* 1997;**388:**235.
17. Akerstedt T, Froberg JE, Friberg Y, Wetterberg L. Melatonin excretion, body temperature and subjective arousal during 64 hours of sleep deprivation. *Psychoneuroendocrinology* 1979;**4:**219–225.
18. DeCoursey PJ. *Chronobiology: Biological Time Keeping*. Sunderland, MA: Sinauer Associates Inc., 2004.
19. Hastings MH. Central clocking. *Trends Neurosci* 1997; **20:**459–464.
20. Gillette MU, Tischkau SA. Suprachiasmatic nucleus: the brain's circadian clock. *Recent Prog Horm Res*. 1999;**54:** 33–58, discussion 9.
21. Reppert SM, Weaver DR. Molecular analysis of mammalian circadian rhythms. *Annu Rev Physiol* 2001;**63:**647–676.
22. Fu L, Lee CC. The circadian clock: pacemaker and tumour suppressor. *Nat Rev Cancer* 2003;**3:**350–361.
23. Scheer FA, Wright KPJr, Kronauer RE, Czeisler CA. Plasticity of the intrinsic period of the human circadian timing system. *PLoS ONE* 2007;**2:**e721.
24. Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. *Science* 2002;**295:**1070–1073.
25. Skene DJ, Arendt J. Human circadian rhythms: physiological and therapeutic relevance of light and melatonin. *Ann Clin Biochem* 2006;**43:**344–353.
26. Mendoza J. Circadian clocks: setting time by food. *J Neuroendocrinol* 2007;**19:**127–137.
27. Khalsa SB, Jewett ME, Cajochen C, Czeisler CA. A phase response curve to single bright light pulses in human subjects. *J Physiol* 2003;**549:**945–952.
28. Paul M, Miller JC, Love RJ, Lieberman H, Blazeski S, Arendt J. Timing light treatment for eastward and westward travel preparation. *Chronobiol Intern* 2009;**26:**867–890.
29. Dumont M, Benhaberou-Brun D, Paquet J. Profile of 24-h light exposure and circadian phase of melatonin secretion in night workers. *J Biol Rhythms* 2001;**16:**502–511.
30. Gibbs M, Hampton S, Morgan L, Arendt J. Adaptation of the circadian rhythm of 6-sulphatoxymelatonin to a shift schedule of seven nights followed by seven days in offshore oil installation workers. *Neurosci Lett* 2002;**325:** 91–94.
31. Martin SK, Eastman CI. Medium-intensity light produces circadian rhythm adaptation to simulated night-shift work. *Sleep* 1998;**21:**154–165.
32. Revell VL, Eastman CI. How to trick mother nature into letting you fly around or stay up all night. *J Biol Rhythms* 2005;**20:**353–365.
33. Crowley SJ, Lee C, Tseng CY, Fogg LF, Eastman CI. Complete or partial circadian re-entrainment improves performance, alertness, and mood during night-shift work. *Sleep* 2004;**27:**1077–1087.
34. Smith MR, Eastman CI. Night shift performance is improved by a compromise circadian phase position: study 3. Circadian phase after 7 night shifts with an intervening weekend off. *Sleep* 2008;**31:**1639–1645.
35. Czeisler CA, Johnson MP, Duffy JF, Brown EN, Ronda JM, Kronauer RE. Exposure to bright light and darkness to treat physiologic maladaptation to night work. *N Engl J Med* 1990;**322:**1253–1259.
36. Maywood ES, O'Neill J, Wong GK, Reddy AB, Hastings MH. Circadian timing in health and disease. *Prog Brain Res* 2006;**153:**253–269.
37. Viola AU, Archer SN, James LM *et al*. PER3 polymorphism predicts sleep structure and waking performance. *Curr Biol* 2007;**17:**613–618.
38. Archer SN, Robilliard DL, Skene DJ *et al*. A length polymorphism in the circadian clock gene Per3 is linked to delayed sleep phase syndrome and extreme diurnal preference. *Sleep* 2003;**26:**413–415.
39. Zhu Y, Brown HN, Zhang Y, Stevens RG, Zheng T. Period3 structural variation: a circadian biomarker associated with breast cancer in young women. *Cancer Epidemiol Biomarkers Prev* 2005;**14:**268–270.
40. Filipski E, Li XM, Levi F. Disruption of circadian coordination and malignant growth. *Cancer Causes Control* 2006;**17:**509–514.
41. Arendt J. *Melatonin and the Mammalian Pineal Gland*. Bristol: Chapman Hall, 1995.
42. Arendt J, Skene DJ. Melatonin as a chronobiotic. *Sleep Med Rev* 2005;**9:**25–39.
43. Arendt J. Melatonin: characteristics, concerns, and prospects. *J Biol Rhythms* 2005;**20:**291–303.
44. Stevens RG, Davis S. The melatonin hypothesis: electric power and breast cancer. *Environ Health Perspect* 1996;**104(Suppl. 1):**135–140.
45. Gibbs M, Hampton SH, Morgan L, Arendt J. *Effect of Shift Schedule on Offshore Shift Workers' Circadian Rhythms and Health*. Health and Safety Executive, 2004. Report No.: 318. http://www.hse.gov.uk/research/rrhtm/rr318.htm
46. Marie Hansen A, Helene Garde A, Hansen J. Diurnal urinary 6-sulfatoxymelatonin levels among healthy Danish nurses during work and leisure time. *Chronobiol Int* 2006;**23:** 1203–1215.
47. Gibbs M, Hampton S, Morgan L. Predicting circadian response to abrupt phase shift: 6-sulphatoxymelatonin rhythms in rotating shift workers offshore. *J Biol Rhythms* 2007;**22:**368–370.
48. Koller M, Harma M, Laitinen JT, Kundi M, Piegler B, Haider M. Different patterns of light exposure in relation to melatonin and cortisol rhythms and sleep of night workers. *J Pineal Res* 1994;**16:**127–135.
49. Boivin DB, James FO. Light treatment and circadian adaptation to shift work. *Ind Health* 2005;**43:**34–48.
50. Burgess HJ, Sharkey KM, Eastman CI. Bright light, dark and melatonin can promote circadian adaptation in night shift workers. *Sleep Med Rev* 2002;**6:**407–420.

51. Folkard S. Do permanent night workers show circadian adjustment? A review based on the endogenous melatonin rhythm. *Chronobiol Int* 2008;**25:**215–224.
52. Axelsson J, Akerstedt T, Kecklund G, Lowden A. Tolerance to shift work—how does it relate to sleep and wakefulness? *Int Arch Occup Environ Health* 2004;**77:**121–129.
53. Kecklund G, Akerstedt T. Effects of timing of shifts on sleepiness and sleep duration. *J Sleep Res* 1995;**4:**47–50.
54. Arendt J, Middleton B, Williams P, Francis G, Luke C. Sleep and circadian phase in a ship's crew. *J Biol Rhythms* 2006;**21:**214–221.
55. Groeger JA, Zijlstra FR, Dijk DJ. Sleep quantity, sleep difficulties and their perceived consequences in a representative sample of some 2000 British adults. *J Sleep Res* 2004;**13:**359–371.
56. Rajaratnam SM, Middleton B, Stone BM, Arendt J, Dijk DJ. Melatonin advances the circadian timing of EEG sleep and directly facilitates sleep without altering its duration in extended sleep opportunities in humans. *J Physiol* 2004;**561**(Pt 1):339–351.
57. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999;**354:** 1435–1439.
58. Van Cauter E, Shapiro ET, Tillil H, Polonsky KS. Circadian modulation of glucose and insulin responses to meals: relationship to cortisol rhythm. *Am J Physiol* 1992;**262**(4 Pt 1): E467–E475.
59. Van Cauter E, Spiegel K, Tasali E, Leproult R. Metabolic consequences of sleep and sleep loss. *Sleep Med* 2008;**9(Suppl. 1):**S23–S28.
60. Lockley SW, Landrigan CP, Barger LK, Czeisler CA. When policy meets physiology: the challenge of reducing resident work hours. *Clin Orthop Relat Res* 2006;**449:**116–127.
61. Holzberg D, Albrecht U. The circadian clock: a manager of biochemical processes within the organism. *J Neuroendocrinol* 2003;**15:**339–343.
62. Lund J, Arendt J, Hampton SM, English J, Morgan LM. Postprandial hormone and metabolic responses amongst shift workers in Antarctica. *J Endocrinol* 2001;**171:**557–564.
63. Holmback U, Forslund A, Forslund J *et al*. Metabolic responses to nocturnal eating in men are affected by sources of dietary energy. *J Nutr* 2002;**132:**1892–1899.
64. Biggi N, Consonni D, Galluzzo V, Sogliani M, Costa G. Metabolic syndrome in permanent night workers. *Chronobiol Int* 2008;**25:**443–454.
65. Scott EM, Carter AM, Grant PJ. Association between polymorphisms in the Clock gene, obesity and the metabolic syndrome in man. *Int J Obes (Lond)* 2008;**32:**658–662.
66. Turek FW, Joshu C, Kohsaka A *et al*. Obesity and metabolic syndrome in circadian Clock mutant mice. *Science* 2005;**308:**1043–1045.
67. Midwinter MJ, Arendt J. Adaptation of the melatonin rhythm in human subjects following night-shift work in Antarctica. *Neurosci Lett* 1991;**122:**195–198.
68. Ross JK, Arendt J, Horne J, Haston W. Night-shift work in Antarctica: sleep characteristics and bright light treatment. *Physiol Behav* 1995;**57:**1169–1174.
69. Ng L, Morgan L, Arendt J. Circadian adaptation in Antarctic shift workers: relationship to diurnal preference, season and subjective sleep. *Chronobiol Intern* 2003;**20:**1162–1164.
70. Barnes RG, Deacon SJ, Forbes MJ, Arendt J. Adaptation of the 6-sulphatoxymelatonin rhythm in shiftworkers on offshore oil installations during a 2-week 12-h night shift. *Neurosci Lett* 1998;**241:**9–12.
71. Barnes RG, Forbes MJ, Arendt J. Shift type and season affect adaptation of the 6-sulphatoxymelatonin rhythm in offshore oil rig workers. *Neurosci Lett* 1998;**252:**179–182.
72. Thorne H, Hampton S, Morgan L, Skene DJ, Arendt J. Differences in sleep, light, and circadian phase in offshore 18:00–06:00 h and 19:00–07:00 h shift workers. *Chronobiol Int* 2008;**25:**225–235.
73. Gibbs M, Hampton S, Morgan L, Arendt J. Predicting circadian response to abrupt phase shift: 6-sulphatoxymelatonin rhythms in rotating shift workers offshore. *J Biol Rhythms* 2007;**22:**368–370.
74. Kelly TL, Neri DF, Grill JT *et al*. Nonentrained circadian rhythms of melatonin in submariners scheduled to an 18-hour day. *J Biol Rhythms* 1999;**14:**190–196.
75. Swerdlow A. *Shift Work and Breast Cancer: A Critical Review of the Epidemiological Evidence*. Norwich: Her Majesty's Stationery Office. Health and Safety Executive, 2003. www.hse.gov.uk/research/rrpdf/rr132.pdf
76. http://www.hse.gov.uk/press/2003/e03132.htm.
77. Straif K, Baan R, Grosse Y *et al*. *Carcinogenicity of Shift-Work, Painting and Fire-fighting. Lancet Oncol* 2007;**8:**1065–1066.
78. Parliamentary Office of Science and Technology, UK, Postnote No.250, 2005, The 24 h Society; IEH (2005) Shift Work and Breast Cancer: Report of an Expert Meeting 12 November 2004 (Web Report W23). Leicester: MRC Institute for Environment and Health. http://www.le.ac.uk/ieh/.
79. Dutch Government Advisory Publication. *Night Work and Breast Cancer: A Causal Relationship?*. The Hague, The Netherlands: Health Council of the Netherlands. http://www.gr.nl (2006, date last accessed).
80. Blask DE, Brainard GC, Dauchy RT *et al*. Melatonin-depleted blood from premenopausal women exposed to light at night stimulates growth of human breast cancer xenografts in nude rats. *Cancer Res* 2005;**65:**11174–11184.
81. Stevens RG, Blask DE, Brainard GC *et al*. Meeting report: the role of environmental lighting and circadian disruption in cancer and other diseases. *Environ Health Perspect* 2007;**115:**1357–1362.
82. Blask DE. Melatonin, sleep disturbance and cancer risk. *Sleep Med Rev* 2009;**13:**257–264.
83. Blask DE, Dauchy RT, Sauer LA, Krause JA, Brainard GC. Light during darkness, melatonin suppression and cancer progression. *Neuro Endocrinol Lett* 2002;**23(Suppl. 2):** 52–56.
84. Gery S, Koeffler HP. The role of circadian regulation in cancer. *Cold Spring Harb Symp Quant Biol* 2007;**72:** 459–464.
85. Lévi F, Schibler U. Circadian rhythms: mechanism and therapeutic implications. *Annu Rev Pharmacol* 2007;**47:**493–528.
86. Czeisler CA, Dijk DJ. Use of bright light to treat maladaptation to night shift work and circadian rhythm sleep disorders. *J Sleep Res* 1995;**4:**70–73.
87. Bjorvatn B, Kecklund G, Akerstedt T. Bright light treatment used for adaptation to night work and re-adaptation back to day life. A field study at an oil platform in the North Sea. *J Sleep Res* 1999;**8:**105–112.

88. Bjorvatn B, Stangenes K, Oyane N *et al*. Randomized placebo-controlled field study of the effects of bright light and melatonin in adaptation to night work. *Scand J Work Environ Health* 2007;**33:**204–214.
89. Smith MR, Fogg LF, Eastman CI. Practical interventions to promote circadian adaptation to permanent night shift work: study 4. *J Biol Rhythms* 2009;**24:**161–172.
90. Mongrain V, Noujaim J, Blais H, Dumont M. Daytime vigilance in chronotypes: diurnal variations and effects of behavioral sleep fragmentation. *Behav Brain Res* 2008;**190:** 105–111.
91. Goel N, Banks S, Mignot E, Dinges DF. PER3 polymorphism predicts cumulative sleep homeostatic but not neurobehavioral changes to chronic partial sleep deprivation. *PLoS One* 2009;**4:**e5874.
92. Chu LW, Zhu Y, Yu K *et al*. Variants in circadian genes and prostate cancer risk: a population-based study in China. *Prostate Cancer Prostatic Dis* 2008;**11:**342–348.