SIMULATION AND FIELD STUDIES OF THE
CIRCADIAN STATUS OF SHIFT WORKERS

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GU2 5XH © Richard G. Barnes 1999
This thesis is dedicated to my wife, Bu, and my parents Lyn and Geoff, whose support has no bounds.
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Summary

There are many problems associated with night shift work, involving both the disruption of social activities and the desynchrony between internal biological clock timing and the forced regimen. Both short term problems (e.g. sleep deficiency, reduced alertness and reduced performance) and potential long term problems (e.g. coronary heart disease and diabetes) may be critically dependent on whether or not the worker is able to adapt to the shift regimen.

In the first of two baseline studies, the 6-sulphatoxymelatonin rhythms of offshore oil workers on a two-week 12-hour night shift (1800h to 0600h) were shown to adapt to the regimen within the first seven days of the shift. The rates of phase shift (mean ± sem) were 1.51 ± 0.16 h/day (n=5), 1.32 ± 0.41 h/day (n=5) and 1.77 ± 0.31 h/day (n=17) for a winter drill crew, winter maintenance crew and summer maintenance crew respectively. The rate of adaptation was not significantly affected by the type of work conducted or the season.

The second baseline study assessed the 6-sulphatoxymelatonin rhythms of offshore drill crews on a one-week day shift (1200h - 0000h), one-week night shift (0000h - 1200h) ‘swing’ shift. A crew studied in winter showed no change in their 6-sulphatoxymelatonin rhythm during night shift, while a crew studied in spring showed a significant phase advance to an acrophase position of 0051h ± 1.7 hours (mean ± sem). This data, together with that of the first baseline study, indicate that both the type of shift and the season influence the direction and degree of adaptation.

A simulation study was conducted to assess the hormonal and metabolic response to a test meal during the first night of night shift (1800h to 0600h). Both plasma glucose and insulin levels were elevated on night shift compared to day shift, suggesting a degree of glucose intolerance during this period. Treatment with bright light (1500 lux) throughout the night shift reduced the glucose intolerance observed and also lowered plasma triacylglycerol levels.

The use of exogenous melatonin to help shift workers acclimatise to day shift following night shift was examined. Exogenous melatonin significantly increased sleep duration compared to placebo. There was also evidence of increased daytime napping and stabilization of sleep onset time under this treatment. While no specific
adaptation rates could be observed, exogenous melatonin did not appear to have an adverse effect on the adaptation of the melatonin and alertness rhythms when taken at the desired bedtime.

The data clearly show that adaptation of the melatonin rhythm to night shift is possible in certain environments. Further evidence of the deleterious effects of night shift on metabolic and hormonal responses to a nighttime meal has been observed, but the use of bright light treatment may be a potential solution to this problem. While the benefits of exogenous melatonin treatment on sleep may be of use offshore, an increased incidence of daytime napping, observed during melatonin treatment, may be of concern for its use in an offshore environment.
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<td>ADP</td>
<td>Adenosine diphosphate</td>
</tr>
<tr>
<td>aMT6s</td>
<td>6-sulphatoxymelatonin</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
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<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>BSA</td>
<td>Bovine serum albumin</td>
</tr>
<tr>
<td>cAMP</td>
<td>Cyclic 3',5'-adenosine monophosphate</td>
</tr>
<tr>
<td>CHO</td>
<td>Carbohydrate</td>
</tr>
<tr>
<td>CSS</td>
<td>Charcoal stripped serum</td>
</tr>
<tr>
<td>CSU</td>
<td>Charcoal stripped urine</td>
</tr>
<tr>
<td>Dab</td>
<td>Double antibody</td>
</tr>
<tr>
<td>DGDW</td>
<td>Double-glass distilled water</td>
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<tr>
<td>EDTA</td>
<td>Ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalograph</td>
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<tr>
<td>GHT</td>
<td>Geniculohypothalamic tract</td>
</tr>
<tr>
<td>HK</td>
<td>Hexokinase</td>
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<tr>
<td>MT</td>
<td>Melatonin</td>
</tr>
<tr>
<td>NAD[H]</td>
<td>Nicotinamide adenine dinucleotide [reduced]</td>
</tr>
<tr>
<td>NEFA</td>
<td>Non-esterified fatty acid</td>
</tr>
<tr>
<td>NGPS</td>
<td>Normal guinea-pig serum</td>
</tr>
<tr>
<td>NSB</td>
<td>Non-specific binding</td>
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<td>PEG</td>
<td>Polyethylene glycol</td>
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<tr>
<td>PRC</td>
<td>Phase response curve</td>
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<tr>
<td>PVN</td>
<td>Paraventricular nucleus</td>
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<td>RHT</td>
<td>Retinohypothalamic tract</td>
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<tr>
<td>SAD</td>
<td>Seasonal affective disorder</td>
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<tr>
<td>SCG</td>
<td>Superior cervical ganglion</td>
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<td>Slow wave sleep</td>
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<td>TAG</td>
<td>Triacylglycerol</td>
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<td>TSH</td>
<td>Thyroid stimulating hormone</td>
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CHAPTER 1

INTRODUCTION
1. Introduction

1.1 Biological rhythmicity

1.1.1 Basis of biological rhythmicity

1.1.1.1 Generation of circadian rhythms

The term ‘circadian’ was first introduced by Halberg (1959) to describe endogenous rhythms with a period of approximately 24 hours, equivalent to that of one solar day. For most living organisms, the most evident environmental change is the alternation between day and night. Since our habits of sleep, rest and activity, work and leisure, eating and drinking, largely follow a routine which is governed by this oscillation, it is not surprising that many physiological, psychological and biochemical processes have an inherent rhythmicity with a frequency similar to that of the solar day. These endogenous oscillations are hence known as circadian rhythms.

The first evidence that specific neuroanatomic sites act as circadian pacemakers was provided by the work of Richter in 1967, and further investigation by Moore and Lenn in 1972 led to the conclusion that the suprachiasmatic nuclei (SCN) of the hypothalamus contained the main pacemaker site (reviewed by Moore-Ede, Czeisler and Richardson, 1983). The SCN is a paired structure of the hypothalamus, lying just above the optic chiasm. There is now strong evidence that the most important role of the SCN is the generation and co-ordination of circadian rhythms (Rusak and Zucker, 1979; Inouye and Kawamura, 1979).

In many organisms, the period of circadian rhythms is slightly more or less than 24 hours, and therefore a mechanism for the daily resetting of the circadian system is needed to maintain synchrony with the day-night cycle in the environment. For organisms with free-running periods of less than 24 hours, each circadian rhythm must be appropriately lengthened, while for those organisms with free-running periods greater than 24 hours, each rhythm must be shortened. This entrainment to a solar day is achieved by perception of environmental time cues, defined by Aschoff in 1954 as zeitgebers. The most reliable index of environmental time is the regular daily alternation of light and darkness, but other examples of zeitgebers include
social cues, meal times, activity and rest, temperature variations, knowledge of clock
time and tidal cycles (in marine organisms).

1.1.1.2 The human circadian system

Early studies in temporal isolation units, where people lived for weeks without
clocks or other time cues, showed that most people ‘free-run’ with a day length of
about 25 hours, with individuals ranging from about 24 hours to 26 hours (Aschoff,
1965; Wever, 1979). In some individuals, ‘spontaneous internal desynchronisation’
ocurred between the sleep-wake cycle and the rhythm of body temperature, so that
the sleep-wake cycle might have a period of approximately 34 hours, whereas the
body-temperature rhythm had a 25 hour period (Wever, 1979; Aschoff and Wever,
1981). It was proposed that human circadian rhythms might be controlled by two
pacemakers; a strong one for temperature and other endogenous rhythms, and a weak
one for rest-activity or sleep-wake (Wever, 1979). This proposal has since been
extended to suggest other oscillators (Folkard et al, 1983), and challenged by others
who have shown that a single oscillator can be responsible for the phenomenon
(Eastman, 1984; Zulley and Campbell, 1985; Daan et al, 1984; Daan and Beersma,

In humans, the SCN is believed to be set to the 24-hour day mainly by the
light-dark cycle. The light information received by the eye is sent to the SCN where
it exerts its synchronising effect. The complex interactions between the environment,
the body clock, and the rhythms that it produces, enable humans to integrate
into a rhythmic environment. Not only are they ‘primed’ during the day and partially
‘shut down’ at night, but their bodies can predict and so prepare for environmental
changes. They can therefore prepare for sleep during the falling phase of adrenaline,
alertness, and core body temperature rhythms, and prepare for the next day as these
rhythms continue beyond their minimum values.

1.1.2 Endogenous circadian rhythms

1.1.2.1 Temperature

In human beings, under natural conditions of lighting and social interaction
(daytime activity 0700-2300h), core body temperature rises to a maximum in the
evening (about 2000h) and then decreases to a minimum in the early morning (about 0400h) (Refinetti and Menaker, 1992). In early isolation experiments with constant illumination and no external time cues, the core body temperature rhythm in humans was shown to free-run, with an amplitude that was only slightly diminished and with a period of about 25 hours (Aschoff et al, 1967). More recent studies have reported an endogenous free-running period in the range of 24.1 to 24.4 hours (Campbell et al, 1993; Czeisler et al, 1995a; Middleton et al, 1997). Core body temperature is commonly used in both normal and isolation studies as a clearly defined marker of circadian rhythms, although its susceptibility to masking (for example by exercise) must be taken into account.

1.1.2.2 Sleep-wake cycle

Several different methods have been employed to study sleep-wake rhythms. Most information is available from sleep deprivation and isolation studies. Sleep deprivation studies have shown that superimposed on the general sensation of increased fatigue, there is a marked circadian rhythm, with a peak during the middle of the normal sleep period and a minimum about the middle of the waking day. Isolation experiments have shown that under free-running conditions, the sleep-wake cycle generally has a period in excess of 24 hours (usually about 25 hours), similar to other endogenous rhythms (for example, temperature) under the same conditions (Wever, 1979). However, in approximately one-third of cases spontaneous internal desynchronisation occurred resulting in a sleep-wake period of up to 33 hours. More recent evidence has shown that sleep tendency and duration are related to circadian phase, with the major peak in sleep tendency and duration occurring around the temperature minimum and the nadir occurring around the temperature maximum (Czeisler et al, 1980; Åkerstedt, 1984). Strogatz et al (1987) have also shown this relation, but indicated a second peak in sleep tendency occurring approximately nine hours after the temperature minimum.

Assessing if a sleep period is good or poor can be done objectively, by electroencephalograph (EEG) recording or actigraphy, or subjectively by sleep questionnaire. Åkerstedt et al (1993) compared the two methods by looking at individuals over a period when sleep was taken at different times. It was found that
objectively, sleep quality was higher when sleep efficiency was higher, slow wave sleep (SWS) energy was lower, and sleep was taken near the temperature trough. Subjectively, a good, ‘deep’ sleep was one that made most use of the time available, was unbroken, and taken towards the temperature trough. A subjectively good, ‘refreshing’ sleep occurred near the temperature peak and may have been rated so because it would be easier to wake up and become alert at that point. Therefore it appears that best sleep is probably that taken around the temperature minimum which in most individuals, under a normal light-dark cycle, would be during the night.

1.1.2.3 Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) was first isolated by Lerner et al (1958) from cow pineal glands. It is synthesised in the pineal gland from tryptophan, via serotonin by hydroxylation and decarboxylation (Axelrod, 1974). The enzyme N-acetyltransferase converts serotonin to N-acetylseryotonin (Weissbach et al, 1961), and it is this reaction that is the rate limiting step (Klein and Weller, 1970). N-acetylseryotonin is converted to melatonin in the final step catalysed by hydroxy-O-methyltransferase (Axelrod and Weissbach, 1960).

The idea that melatonin synthesis could be controlled by light had been considered for many years (for example Wurtman et al, 1964) although its mechanism was not elucidated. Lewy et al (1980) showed that bright, artificial light suppressed the nocturnal secretion of melatonin in humans. The effect of light is now known to act via the SCN. Berk and Finklestein (1981) showed that projections from the SCN led to the superior cervical ganglion (SCG), via the paraventricular nucleus (PVN) of the hypothalamus. Sympathetic nerves from the SCG are able to release noradrenaline which then acts on the adrenergic receptors on the pineal gland cell membrane. The activity of the SCN, in response to light, results in the inhibition of noradrenaline release at the pineal. In the absence of light the released noradrenaline acts on the adrenergic receptors on the pineal membrane which produce an increase in cyclic 3',5'-adenosine monophosphate (cAMP), and this in turn causes an increase in N-acetyltransferase activity (Klein and Moore, 1979). The increased activity results in increased melatonin production and hence melatonin can be thought of as a hormone associated with darkness.
Melatonin secretion has a definite 24-h rhythm, with low levels during the day, an onset in the late evening, and a peak around 0200h followed by a gradual return to daytime levels (Arendt et al, 1977). In the absence of a light-dark cycle (for example in the blind) it has been shown to have an endogenous rhythm of around 25h (24.7 hours - Lewy and Newsome, 1983; 24.34 to 24.79 hours - Lockley et al, 1997a). One of the best and non-invasive ways of measuring melatonin production is to measure its urinary metabolite 6-sulphatoxymelatonin (Kveder and McIssac, 1961), which is a good index of plasma melatonin secretion in both timing and amplitude (Bojkowski et al, 1987a).

At present the main function of melatonin is considered to be as a photoperiodic signal. Changing duration of melatonin reflects day length and this information is used for the organisation of photoperiod dependent functions. For instance, the increased duration of melatonin secretion during shortening photoperiods stimulates the reproductive system of seasonally breeding animals such as ewes (Bittman et al, 1983; Bittman and Karsch, 1984; Yellon et al, 1985) and goats (Deveson et al, 1992). Although humans may not have this form of seasonality, the duration of melatonin secretion in humans has been shown to be longer during short photoperiods and shorter during long photoperiods (Wehr, 1991; Burešová et al, 1992).

1.1.2.4 Alertness and performance

Early studies showed that there is a 24-h rhythm of performance, with most performance curves being parallel to the 24-hour body-temperature rhythm (Kleitman, 1939 revised 1963). Kleitman suggested that temperature was possibly the main factor involved, with mental processes being chemical reactions in themselves, or dependent upon metabolic activity. Blake (1967) also showed a time of day effect on various tasks, again relating it closely to the body temperature rhythm, although some tasks showed no significant improvement throughout the day. More recent studies have developed a multi-oscillatory model for human performance tasks (Folkard et al, 1983; Monk et al, 1983; Monk et al, 1984), by forcing internal desynchronisation of the temperature and sleep-wake cycle to different periods under temporal isolation. For example, in one study manual dexterity tasks appeared to
depend only on the temperature oscillator, while verbal reasoning tasks depended on both sleep/wake and temperature oscillators (Monk et al, 1983). The conclusion of these studies is that different types of performance tasks can exhibit different circadian rhythms, possibly due to them being under the control of separate oscillators.

Subjective alertness appears to have a diurnal rhythm similar to that of performance, generally running in parallel with the core body temperature rhythm, and appears to be under the control of both the sleep/wake and temperature oscillators (Monk et al, 1989). More recent evidence has indicated that subjective alertness and cognitive performance may be dependent both on the duration of prior wakefulness and circadian phase, with lowest alertness and performance occurring when prior wakefulness of greater than 16 hours duration coincides with the falling limb of the temperature rhythm (Dijk et al, 1992).

1.1.2.5 Glucose, insulin and gut hormones

Much of the recent work looking at the circadian rhythmicity of glucose and insulin has been done by Van Cauter et al. Under rest conditions, with continuous glucose infusion, plasma glucose levels have been shown to gradually rise throughout the day to a peak in the early hours of the morning (Van Cauter et al, 1989). This rise was not influenced by the rate of glucose infusion or the timing of infusion initiation. Thus a circadian rhythm in glucose intolerance was seen, with an average peak at 0340h. However, this study did not consider the effects of sleep on these parameters. A further study was therefore conducted to examine the effects of night and day sleep (Van Cauter et al, 1991). The expected rise of glucose levels during a night of sleep deprivation was also seen during night sleep and day sleep. Insulin levels paralleled those of glucose, except that during sleep deprivation only half the subjects showed a night time rise. These results suggest that both circadian rhythmicity and sleep modulate glucose regulation. The results of a study using mixed meals confirmed the above findings, with the glucose response being greater following an evening meal than following a morning meal (Van Cauter et al, 1992).

The work on gut hormones is strictly limited to changes during shift work and will be discussed later (section 1.2.1.6)
1.1.3 Entrainment and phase-shifting of circadian rhythms

1.1.3.1 The light/dark cycle

The importance of the light-dark cycle for circadian synchronisation in humans was originally discounted in the isolation experiments of Aschoff and Wever. They inferred from their studies that social factors were the principal synchronisers of the circadian pacemaker (Aschoff, 1965; Wever, 1979). The audible gong system they used to signal urine collection time was considered to be the social zeitgeber. The problem with these studies was that the subjects were able to control their own light exposure, having full access to desk and bed-side lamps, as well as lighting in the kitchen area.

Follow up experiments with stricter control over lighting and social cues showed that the light-dark cycle was able to entrain the rhythms of temperature and activity (Czeisler et al, 1981). There was still some debate, however, concerning whether the physical effects of the light, or the behavioural effects of the light-dark cycle, were causing entrainment (Wever et al, 1983). Further studies were carried out to try to separate out the two potential zeitgebers, using a protocol which increased the period of the light-dark cycle from 26 hours to 29 hours over the course of 4 weeks. When 1000 lux intensity was used during the light stage the upper entrainment limit of the temperature rhythm reached 26.91 ± 0.24 hours. When a light intensity of 4000 lux was used, the period of 29 hours was within the range of entrainment. This indicated that the physical effect of light was causing entrainment at the higher intensity since the behavioural effect was considered to be the same between the two studies (Wever et al, 1983).

Further evidence to support the importance of the light-dark cycle arose from studies looking at totally blind people. It was shown that the diurnal rhythms of renal output (Loban and Tredre, 1963), sleep tendency (Miles et al, 1977) and cortisol secretion (Orth et al, 1979) were not entrained to the 24 hour day in some blind subjects when living on a 24 hour schedule. This lack of entrainment occurred even in the presence of strong activity and social cues in the latter two studies. The results of these studies have since been confirmed for sleep, melatonin, cortisol and

The failure to demonstrate a suppressant effect of domestic lighting on melatonin synthesis in early studies supported the overall lack of a light-dark influence on circadian rhythmicity (Arendt et al, 1977). However, Lewy et al (1980) showed that artificial bright light exposure between 0200h and 0400h at an intensity of 1500 lux was capable of suppressing melatonin synthesis, and that increasing the intensity to 2500 lux increased the suppression. A further dose-response relationship between light intensity and melatonin suppression was shown from intensities as low as 300 lux up to 2500 lux when given between 0030h and 0100h (Bojkowski et al, 1987b). The intensity of light required to phase shift the circadian pacemaker was considered to be much higher that that needed for melatonin suppression, with intensities up to 10,000 lux of three hours duration around the temperature minimum showing no phase shift even when melatonin was suppressed by an intensity of 500 lux (Hashimoto et al, 1996). However, Broadway et al (1987) showed a phase advance of the melatonin rhythm in the Antarctic during winter, using a light intensity of 2500 lux in the form of a skeleton photoperiod (light pulses between 0800h and 0900h in the morning, 1930h and 2030h in the evening). More recently, Boivin et al (1996) have shown phase-shifting of the core body temperature with a light intensity as low as 180 lux, and a non-linear dose relationship of increasing phase shift (+1.16 ± 0.96 h to +4.49 ± 0.36 h) with increasing light intensity (180 lux to 9,500 lux). The treatment was initiated one hour before the core body temperature minimum and lasted for five hours.

Light entrains circadian rhythms by its ability to phase shift the SCN in either an advancing or delaying direction, depending on its timing and duration of exposure. This resetting effect occurs independently of sleep-wake and social schedules (Czeisler et al, 1986; Lewy et al, 1986; Drennan et al, 1989). Further work by Czeisler et al (1989) has shown that three cycles of high intensity light (7,000 - 12,000 lux) phase advance the temperature rhythm when centred just after the temperature minimum, and phase delay when centred just before the temperature minimum. The smallest phase shifts occur during the subjective day, and the period
around the temperature minimum is considered to be the most sensitive to light induced phase-shifts (Czeisler et al, 1989). The acute phase-shifting effects of light have also been shown using core temperature as a marker rhythm (Minors et al, 1991). Advances of the melatonin rhythm between 0.6 and 2.6 hours after a single exposure of bright light (3000 lux) between 0300h and 0900h have been shown (Burešová et al, 1991).

The relationship between the timing of a light pulse and the resulting phase-shift of endogenous rhythms can be expressed as a phase-response curve (PRC). The first PRC to light in humans was shown by Czeisler et al (1989) in the study mentioned above, with volunteers on a fixed sleep-wake schedule. However his three-cycle protocol meant that each light pulse was given at the same time of day even though circadian time was being successively phase-shifted. Minors et al (1991) conducted a similar study, except using a single three hour light pulse (5000 - 9000 lux), and volunteers selected their own sleep-wake times under free-running conditions. The results agreed with previous studies; centering the light pulse slightly before temperature minimum caused a phase delay of body temperature, while centring it after the minimum caused a phase advance. Another PRC to light, using plasma melatonin and thyroid stimulating hormone (TSH) as the phase markers, was shown by Van Cauter et al (1994). The study was run under constant routine conditions, thereby removing any masking effects produced by sleep and a light-dark cycle, using a three hour light pulse of 5,000 lux intensity. The resulting PRC not only agreed with the other two studies, but also showed that the magnitude of phase shift was greater in the delaying direction than in the advancing direction. Figure 1-1 shows the published PRCs produced by Minors et al (1991) and Van Cauter et al (1994).

Light can only entrain endogenous circadian rhythms within a limited range, centred about the free-running period (Wever, 1979; Wever, 1983). Attempts to entrain outside this period (longer or shorter) result in the desynchronisation of the endogenous rhythms from the imposed period, and a return to the free-running tau (Arendt et al., 1985). The limit of entrainment does however depend on the strength
Figure 1-1. Phase response curves to light.

Phase response curves to light using plasma melatonin and TSH (— ), and core body temperature (— — ) as markers of circadian rhythm status. Dashed line (— — — ) indicates where no estimation was made. Redrawn from Minors et al (1991) and Van Cauter et al (1994).
of the light stimulus, with increasing light intensities increasing the range of

The exact mechanism of circadian entrainment by light is still unknown.
While the pathways from the retina to the SCN have been established (see below),
the circadian perception of light in the retina itself is far from clear.
Czeisler et al (1995b) have shown that visual light perception is not required for melatonin
suppression with light, and suppression also does not appear to be influenced by
colour vision deficiencies (Ruberg et al, 1996). The spectral qualities of light needed
to suppress melatonin were studied by Brainard et al (1985) using a one hour pulse of
patternless monochromatic light at various wavelengths (448-604 nm). While all
wavelengths produced suppression to some degree, the 509 nm wavelength produced
the largest effect with 64% suppression over baseline. It must be noted, however,
that melatonin suppression does not necessarily imply an ability to entrain.

The SCN receives entraining information via at least two pathways; the
retinohypothalamic tract (RHT), which is thought to be the main pathway for photic
entrainment (Moore and Card, 1985; Johnson et al., 1988a), and the
geniculohipothalamic tract (GHT), which potentiates RHT photic entrainment and is
thought to be the main pathway of non-photic entrainment (Johnson et al, 1988b;
Mrosovsky, 1995). Destruction of these pathways has been shown to cause a loss of
entrainment with a consequent change to a free-running state (Rusak, 1977). The
neurotransmitters thought to be involved with photic transmission in the RHT are
 glutamate (Meijer et al, 1988) and acetylcholine (Earnest and Turek, 1985; Keefe et
al, 1987), while neuropeptide Y is thought to be the main neurotransmitter in the GHT
(Moore and Speh, 1993).

1.1.3.2 Non-photic zeitgebers

It is well established that most mammals can be entrained by zeitgebers other
than the light dark cycle. For example, hamsters can be entrained by forced exercise
(Mistlberger, 1991; Mrosovsky et al, 1992), feeding patterns (Mistlberger, 1991) and
social interaction (Mrosovsky, 1988). The effect of non-photic zeitgebers on the
human circadian system, however, is far from clear.
There is very limited data on the entrainment of circadian rhythms by exercise in humans. The two most notable studies have shown large phase shifts in the circadian rhythms of melatonin and temperature under constant routine (Van Reeth et al, 1994) and simulated shift work (Eastman et al, 1995) protocols respectively, when exercise was positioned around the temperature minimum at night. Current evidence suggests that exercise at any other time has no significant influence on circadian rhythms (Buxton et al, 1997).

A possible zeitgeber effect of activity, social interaction and/or the imposed sleep-wake cycle is seen in humans in the Antarctic. Workers on research bases maintain synchrony with their work environment when on strict regimens, even during winter when light levels do not rise above 500 lux and there is no natural light (Broadway et al, 1987; Midwinter and Arendt, 1991; Ross et al, 1995). However, workers in a similar location who are not kept to a strict schedule free-run (Kennaway and Van Dorp, 1991). This suggests that the enforced regimen in the former studies may have caused the entrainment observed.

Exogenous melatonin has the ability to phase shift the endogenous melatonin rhythm of healthy humans under a normal light-dark cycle, when taken at 1700h (2mg dose) (Arendt et al, 1985; Wright et al, 1986) or 2200h (8mg dose) (Mallo et al, 1988). This has also been shown in free-running blind individuals (Sack et al, 1991). Melatonin has now been shown to phase shift circadian rhythms according to a phase response curve, which is similar to, but almost the inverse of the PRC for light. Three such PRCs have been produced by Zaidan et al (1994), using 20 μg infusion for three hours, Lewy et al (1992) using two 0.25 mg doses consolidated (or 0.5 mg acute doses) over two hours and Middleton et al (1997) using 5 mg in free-running conditions. The resulting PRCs showed delays when melatonin was administered in 'circadian' morning and advances when administered during 'circadian' afternoon/early evening. It has been suggested that the phase-shifting effects of melatonin may be associated with core body temperature suppression, due to the correlation between the magnitude of melatonin (5 mg) induced temperature suppression and the degree of phase shift of melatonin onset time (Deacon et al, 1994). There is very limited data, however, on the entraining effects of melatonin.
Entrainment was reported in one blind subject (Sack et al, 1991), and sleep can be stabilised to a 24 h period by melatonin in both blind and sighted free-running subjects (Arendt et al, 1988; Middleton et al, 1997).

1.1.4 Masking

'Masking' is any process that distorts the original output from the internal clock, whether it originates from inside or outside the body. Masking influences include sleep, waking, exercise, meals and stress and can result in the unreliable estimation of the circadian time of the internal biological clock (Minors and Waterhouse, 1989).

A good example of masking is the effect of the sleep-wake cycle on core body temperature. Wever (1985) demonstrated that individuals in temporal isolation, whose core body temperature rhythms and sleep-wake rhythms were desynchronised, had higher core body temperature when awake than in the same phase position when asleep. Another masking effect on core body temperature is activity/exercise, obviously increasing temperature with increasing activity.

Minors and Waterhouse (1989) suggested two possible methods of eliminating masking effects; changing the experimental design to remove the masking effects or correcting the masking effects by mathematical analysis. While the former method may put limitations on the experimental protocol, the latter is based on theoretical models which could be incorrect in abnormal situations. Härma et al (1994a) have stressed the importance of taking masking effects into account following a study on nurses undergoing rotating shift work. The shift in core body temperature rhythm was calculated by three different methods, after the second day of night shift, and showed a 6.3h delay according to cosinor analysis, a 6.2h delay according to a cross-correlation method, but only 1.7h delay following demasking. Considering that very few if any circadian rhythms would adapt more than two hours per day in such a schedule it is clear that the effect of masking greatly overestimated the degree of phase shift.

By far the best method of assessing circadian phase is to concentrate on circadian rhythms that are least likely to be masked in the chosen experimental design.
1.1.5 Factors affecting circadian rhythms

1.1.5.1 Diurnal type

An increasing number of studies now consider the diurnal type of subjects as well as the specific parameters under investigation. This refers to whether a subject's social habits tend towards early bed time and early rising (morning or 'M' type) or late bed time and late rising (evening or 'E' type). Diurnal type can be estimated by a self-assessment questionnaire which has been validated by Horne and Östberg (1976). They looked at 48 subjects who rated themselves as moderate to definite morning types (n=18), moderate to definite evening types (n=20), or intermediate types (n=10) on the basis of the questionnaire. The oral temperature profiles of the morning types showed a peak about an hour earlier than the evening types, but this may just have been due to the relative bed times. A more important observation was that the morning types displayed a relatively rapid waking temperature rise, while the evening types tended to display a steady temperature rise from waking with no post-lunch dip.

1.1.5.2 Diurnal activity

Binkley (1993) showed that humans tend to display a 7-day variation in their activity patterns associated with weekly work and leisure routines. The data indicated that on weekends, in subjects who only worked during the week, there was a phase delay of activity onset of about 2.1 hours and also a delay in activity acrophase of about 1.5 hours. This is a common trait in many individuals and is the most likely cause of 'Monday morning blues', where the forced advanced sleep offset can cause considerable disruption.

1.1.5.3 Alcohol

The effects of alcohol on human circadian systems have mainly concentrated on melatonin synthesis. Röjdmark et al (1993) studied the effects of placebo and two concentrations of ethanol (0.34 g/kg and 0.52 g/kg body weight), administered at 1800h, 2000h and 2200h, in seven subjects. The results indicated that melatonin synthesis throughout the night was reduced in a dose dependent fashion by ethanol. A similar study by Ekman et al (1993) has also shown this effect of ethanol at slightly higher levels of 0.5 and 1 g/kg body weight. Both studies suggest that this action on melatonin synthesis may result in potential sleep disruption, at least during the early
sleep stages. It is important to note, however, that the effects of alcohol may be acute rather than circadian.

There have been no reported phase shifting effects of alcohol to date. Its action on melatonin synthesis does, however, lead to some interesting hypotheses. As mentioned earlier, the melatonin rhythm may exert a time cue effect on the biological clock, possibly via the timing of onset or acrophase. Administration of alcohol just before melatonin onset would lead to acute inhibition of melatonin synthesis and hence an apparent delayed onset. If the effect of alcohol were to continue beyond initial melatonin onset, it could reduce the amplitude and delay the melatonin peak. Both events could be misinterpreted as a delayed melatonin rhythm.

1.1.5.4 Drugs

The drugs of most relevance in shift work studies are those that are either used frequently, such as non-steroidal anti-inflammatory drugs (NSAIDs), or those that are used specifically for shift work complaints, such as benzodiazepines for sleep problems. Hence, these two drug classes will be discussed in this section.

The most commonly used NSAIDs are aspirin and ibuprofen. In two studies by Horne et al (1980b, 1989), aspirin (600 mg) given three times a day produced a small fall in oral temperature during time awake and significantly decreased SWS and increased stage 2 sleep. The method of action may possibly have been an antipyretic effect since SWS may be affected by waking temperature, or prostaglandin (PG) suppression since PGs may be modulators of sleep (Naito et al, 1988). A further study looked not only at aspirin (650 mg) but also acetaminophen (650 mg) and ibuprofen (400mg) on the daytime and night-time sleep of 37 individuals (Murphy et al, 1992). This study also showed night-time sleep disruption, with the NSAIDs causing decreased sleep efficiency, an increased number of awakenings and longer latency to SWS. There were no effects on daytime sleep however. A possible explanation could relate to melatonin suppression during the night-time sleep (as seen by Bird et al, 1986) as a contributing factor to sleep disruption, whereas melatonin would already be low during the daytime sleep. It must be noted however that while the NSAIDs were administered immediately prior to the night-time sleep period, they
were given early in the morning for the afternoon sleep period. Hence the afternoon sleep period may have been too late for the effects of the drugs.

A study looking at day and night-time body temperature showed that aspirin and ibuprofen increased night-time tympanic temperature, while ibuprofen had no effect during the day. Together with the work of Bird et al (1986), this led to the conclusion that melatonin and body temperature were inversely affected by NSAIDs. This was taken further to suggest that since PGs were probably involved in melatonin synthesis and thermoregulation, they may be at the beginning of the causal chain linking melatonin, body temperature and sleep. No studies have reported any evidence of a phase-shifting ability of NSAIDs.

Most studies on benzodiazepines have looked at their effects on sleep and subsequent alertness, performance and mood. For example, a study by Bonnet et al (1988) looked at the effects of varying amounts of triazolam on sleep and subsequent performance during a simulated night shift. EEG patterns were measured following administration of either placebo, 0.125mg, 0.25mg or 0.5mg of triazolam at 1130h before a bedtime of 1200h, and performance tasks were run from 2300h for a 10 hour work shift. The results showed that day sleep and subsequent alertness, performance and mood were all increased in a dose-related fashion. Another study by Nicholson et al (1986) looked at the effect of brotizolam on sleep following eastward and westward transmeridian flight. The results indicated that brotizolam improved sleep on the first night after westward travel and on the second night following eastward travel. Both studies indicate the therapeutic potential of benzodiazepines under conditions where sleep must be taken at an abnormal phase.

While there are many studies showing the phase-shifting abilities of benzodiazepines in animals (e.g. Ralph and Menaker, 1986; Turek and Losee-Olson, 1986) there is little evidence for this effect in humans. Moreover in animals, the observed phase-shifts after triazolam are dependent on induced activity (Mrosovsky and Salmon, 1990). Usui (1994) reported that triazolam (0.5mg) phase advanced the body temperature rhythms of 6 male subjects significantly compared to placebo. However, their bedtimes and rising times were deliberately advanced by 3 hours, so the effect of triazolam may have been via its reinforcing effect on sleep.
1.2 Disorders of biological rhythms

1.2.1 Shift work

1.2.1.1 Shift work schedules

When discussing the benefits of one particular shift schedule compared with another it is important to consider whether a shift in biological rhythms is an advantage or a disadvantage. To the employer, the performance of the work force is important and thus a complete shift into the new schedule would be theoretically desirable. To the employee, however, working a rapid rotation (i.e. a few days on night shift followed by a few days off), a lack of phase shift is of benefit for the subsequent rest days. In extreme situations, such as that of ambulance personnel on 24-hour duty, circadian adaptation was reduced compared with a more regular 8-hour schedule (Motohashi and Takano, 1993). This may be due more to frequent napping on long shifts which would not be allowed during the shorter schedule. In most studies of rapidly rotating shifts there is little or no adaptation of circadian rhythms (for example Costa et al, 1994; Roden et al, 1993). Koller et al (1994) have shown that shift workers who avoid light following night work are able to phase delay their salivary melatonin acrophases compared to the same workforce exposed to morning light. Therefore, the lack of phase shift seen in the previous studies may be due to the effect of morning light resetting the circadian pacemaker to the normal light-dark cycle.

The long term effects of different shift systems were studied by Rosa (1993a). They looked at performance and alertness on 8-hour and 12-hour rotating shifts in natural gas utility workers over a period of months. The results suggested that after 10 months on 12-hour shifts alertness and total sleep time across the workweek were considerably reduced compared to 8-hour shifts. It is interesting to note, however, that the work force preferred the 12-hour shift system because of the extra time off compared to the 8-hour shift system, and were prepared to put up with the extra sleep loss.

The direction of the shift in shift work may also be an important factor. A study by Barton and Folkard (1993) showed that in an advancing system, poorer physical and psychological health, more sleep disruption, more social and domestic
disruption, and lower job satisfaction occurred than in a delaying system. It could be speculated that this may be due to the natural tendency of the biological clock to delay in humans, resulting in easier adaptation to a delaying shift. However, when comparing a normal advance shift with an advance shift followed by a quick return (to day shift work), it was the quick return that mainly highlighted the above problems. Therefore, a combination of direction and the length of break when changing from one shift to another was the critical factor. Similar sleep problems have been observed in individuals following transmeridian flight, where westward (delay) flights cause fewer sleep problems than eastward (advance) flights (Nicholson et al, 1986).

1.2.1.2 Temperature

The assessment of the endogenous temperature rhythm in shift workers is complicated by masking effects of activity resulting from night work. Early studies by Andlauer et al (1979) suggested that the amplitude of the oral temperature rhythm might act as a marker for tolerance to shift work. In their study they found that workers with large amplitudes were more tolerant to shift work (i.e. less digestive troubles, neurological troubles and sleep alterations). Reinberg et al (1983, 1984) suggested that it was the desynchronisation of the temperature rhythm from the activity-rest rhythm that predicted intolerance to shift work and led to the reduced temperature amplitude. A more recent study by Knauth and Härnäs (1992) has also indicated a large temperature rhythm amplitude in shift workers who rated their health as high, but there was no significant difference in ratings of sleep.

1.2.1.3 Melatonin

The development of melatonin as a marker rhythm now allows more accurate estimations of phase to be made. The lack of any major masking factors other than bright light has led to its use as the main marker rhythm in field studies. Therefore melatonin is now the marker of choice where temperature rhythms were originally used and required complex demasking methods to purify the data.

The effect of shift work on melatonin levels appears to depend on the timing of the shift and the number of consecutive shift days. For example, several studies have shown a phase shift in the melatonin rhythm during night shift (Waldhauser et
al, 1986; Sack et al, 1992b; Costa et al, 1994; Quera-Salva et al, 1996). The study by Waldhauser et al (1986) showed that permanent night shift workers (bakers) adapted their melatonin rhythms to the night shift, but only two subjects were used to show this. Sack et al (1992b) looked at shift workers following a night shift and found that the melatonin peaks had either advanced or delayed to varying degrees. The varying peak times were thought to be due to age differences among the workers, but the protocol showed that the workers had been on night shift for different numbers of days before entering the study unit, and were therefore probably at different points of adaptation. The study by Costa et al (1994) did not show a definite phase shift of melatonin, but a decrease in melatonin output during the night was seen on the second day of night shift possibly due to some light suppression. Unfortunately the fast rotation of the shift schedule meant that there were only two night shift days. Quera-Salva et al (1996) showed a rapid shift in the peak of 6-sulphatoxymelatonin in 6 out of 19 nurses following three consecutive night shifts. The average peak in the adapted individuals was around midday while that of the unadapted individuals was around 0600h.

In contrast to the above studies, several studies have indicated no adaptation of the melatonin rhythm to night shift. Touitou et al (1990) showed that after four days of night shift 3 out of 4 night shift workers maintained their plasma melatonin peaks at 0200h. Their peak levels were elevated compared to controls and it was considered that this large amplitude of the rhythm might have anchored their circadian phase positions. A similar study by Roden et al (1993) also showed no difference between the melatonin rhythms of shift workers and controls after six consecutive night shifts.

A possible explanation for the presence or absence of a phase shift in melatonin rhythm was given by Koller et al (1994). In their study looking at different patterns of light exposure in the morning, following night shift, they showed that increasing bright morning light exposure resulted in a decreasing shift in the salivary melatonin acrophases. Therefore, light avoidance at the end of work and on the way home afterwards could lead to significantly better rates of adaptation to the night shift.
1.2.1.4 Sleep

It is generally acknowledged that shift work results in substantial sleep problems (Åkerstedt, 1984; Regestein and Monk, 1991) and that these problems can be long lasting (Åkerstedt and Kecklund, 1991a; Moneta et al, 1996). The subsequent effect of these sleep problems can lead to napping and 'microsleeps' during working hours (Åkerstedt and Torsvall, 1985; Torsvall et al, 1989; Quera-Salva et al, 1996). Studies on the immediate effects of shift work are conflicting, mainly due to the great variety of shift schedules available. Many studies find that both night shifts and morning shifts have the greatest sleep problems, mainly with less sleep and poorer sleep quality (Frese and Harwich, 1984; Åkerstedt et al, 1991b; Fischer et al, 1997), while others found no adverse effect (Costa et al, 1994). Surprisingly some found problems only with evening shifts (Barak et al, 1995). While no obvious explanation can be given for sleep loss following evening shifts which terminate before the usual bedtime, and the short sleep following night shifts can be attributed to circadian factors, the sleep on morning shifts mainly depends on when the shift starts. If the morning shift starts early (for example 0600h) then sleep is reduced because individuals tend not to go to bed any earlier but must get up earlier to get to work (Frese and Harwich, 1984; Budnick et al, 1994). If the morning shift starts later (for example 0700h) then time in bed is greater and hence there is less sleep loss (Costa et al, 1994).

Sleep problems appear to be related to the amount of SWS in the sleep period, with SWS being a priority compared to REM sleep following sleep deprivation (Rotenberg, 1991). It was therefore suggested that alteration of sleep structure might be used as a sign of adaptation or maladaptation to shift work, especially in those who are sensitive to reduced REM sleep (Rotenberg, 1991).

1.2.1.5 Alertness and performance

Budnick et al (1994) compared the subjective alertness patterns of shift workers on a 12-hour rotating shift (0600-1800 and 1800-0600) and found that although alertness was worst on the night shift, the day shift was also quite poor. The conclusion was that while the lowered alertness on night shift was due to its circadian
rhythm, the poor alertness of the day shift workers might have been due to the early start of the shift and the sleep deprivation common in morning shift workers.

Comparisons between injuries on day shift and night shift have led to conflicting results. For example, a study by Novak et al (1990) on chemical plant workers showed no significant differences in rates of injuries between day and night shifts, although this may have been due to the reduced worker density on night shift. In contrast, Gold et al (1992) showed that hospital nurses on rotating shift work were more likely to fall asleep during night work and reported significantly more accidents or errors related to reduced alertness. Also, a study by Smith et al (1994) showed a significant increase in the frequency of injuries from the morning shift, through the afternoon shift, to the night shift in machine-paced workers. In self-paced workers, the increase in injuries was significantly greater during the afternoon and night shifts than during the morning shifts. Considering that sleep had been reported to be worse in morning shift workers than any other shift, the increased injury rates were thought to be mainly due to unadapted performance and alertness rhythms.

A study by Folkard et al (1993a) attempted to separate the endogenous factors influencing performance from exogenous ones. The results suggested that different types of performance might have different rates of adjustment to abnormal work hours, depending on the relative magnitudes of their endogenous and exogenous controls.

1.2.1.6 Glucose, insulin and gut hormones

The effect of shift work on postprandial responses to a mixed meal has been addressed in a simulated study by Hampton et al (1996). They looked at plasma glucose, insulin, glucose-dependent insulino tropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), triacylglycerol (TAG) and non-esterified fatty acids (NEFAs), for 6 hours following a test meal, in nine subjects in their normal environment and following a 9 hour phase advance. A significantly higher post-prandial response of insulin and glucose was observed following the 9 hour phase advance, with the greatest response occurring in the latter half of the 6 hour test period. The postprandial rise in plasma TAG was significantly delayed following the phase advance and continued to rise throughout the study, while the peak during the normal
routine occurred 5 hours postprandially. While plasma NEFA levels fell during the first 3 hours following the test meal in both conditions, the rate of return was significantly delayed in the phase shift condition. There were no differences in postprandial plasma GIP and GLP-1. It was concluded that the observed insulin insensitivity and altered lipid response could result in the development of significant abnormalities (for example coronary heart disease or non-insulin dependent diabetes) in long term shift workers.

1.2.1.7 Diurnal type

The differences in certain types of performance between diurnal types were shown in a study by Horne et al (1980a), looking at detection and rejection of faulty items on a conveyor belt. There were no differences between the groups when looking at the number of perfect items erroneously rejected. There were marked differences, however, in the number of faulty items correctly rejected. The evening types' performance reflected the body temperature profile, with a low level in the morning gradually rising throughout the day to a peak in the evening. However, the morning types displayed a high performance level in the morning which rapidly reduced throughout the day with a marked post-lunch dip, even though the core body temperature profile of the morning types showed a characteristic peak in the evening about one hour before that of the evening types.

Measurements of subjective sleep (Webb and Bonnet, 1978) have shown that evening types not only go to bed later but also take longer naps and have more variable wake up times and total time in bed. Morning types appear more rigid in their sleep patterns, waking when they expect to, more easily and feeling more rested with better sleep quality. This rigidity of sleep patterns observed in morning types has also been seen objectively in EEG studies (Kerkhof and Lancel, 1991; Lancel and Kerkhof, 1991) where a normal day-shift night was compared to three night shift nights. Morning types displayed reduced sleep quality (in terms of REM sleep and SWS) during the night shift day-sleeps compared to the evening types, suggesting that evening types may adapt more easily into a night active, day sleep pattern than morning types.
Further studies have confirmed that morning types have more difficulty adapting to phase shift/shift work than evening types (Honma et al, 1992; Eastman et al, 1995). This is especially the case if the shift regimen is a delaying system, since morning types appear to be naturally phase advanced (Costa et al, 1989).

1.2.1.8 Age related problems

Ageing is considered to lead to a phase advance of the daily sleep episode, a decision to go to bed earlier and arise earlier, and a phase advanced core body temperature profile compared to younger individuals, according to a study by Weitzman et al (1982). Mood states and physical performance measures also appear to peak earlier in the day in older individuals (Atkinson et al, 1992), with lowered amplitudes of rhythms in mood-states correlating with the lowered amplitudes of core body temperature seen previously. Ageing itself leads to worse sleep (in terms of several parameters including sleep efficiency) (Weitzman et al, 1982). However, from the above data it could be considered that old age is fairly analogous to a morning diurnal type in relation to circadian phase positions. The question arises whether the analogy stretches to include adjustment to phase shifts.

A study by Honma et al (1992) looked at the factors influencing adjustment to shift work. The results indicated that while the age difference between two groups (20-30 year olds and 40-50 year olds) had no direct significant effect, adjustment was influenced by different factors in the two groups. In the young group, morningness and fatigue during day shift led to significantly slower adjustment, while in the older group, late arisers and those with frequent awakenings during sleep on day shift took longer to adjust. The lack of any direct significant difference in adaptation rates between the two age groups may have been due to the age gap between the two groups being too small, and/or the range within each group being too large. This can also be seen in a study by Moline et al (1992), where although the middle-aged group (37-52 years old) showed larger decreases in alertness and well-being, and larger increases of waking time during sleep and earlier termination of sleep, the rate of adjustment of the core body temperature rhythm to a simulated 6 hour phase shift did not differ with that of the young group (18-25 years old).
A more representative study of age and its relationship to adjustment to night work was conducted by Hämä et al (1992), looking at three age groups (19-28, 30-44 and 53-59 years old), and again in a later repeat study looking specifically at the oldest and youngest groups (Hämä et al, 1994b). Both studies looked at voluntary letter sorters in a shift work laboratory, experiencing one day shift and then three consecutive night shifts. The first study indicated that by the third night shift day, the minimum of the mean rectal temperature was delayed by 5.9 hours for the youngest group, 3.3 hours for the middle-aged group, and 2.3 hours for the oldest group. The marked increase in salivary melatonin level during the night shift, experienced by all three groups, became less steep in the young group at the end of the three days, suggesting a degree of melatonin phase shifting in this group. Day sleep length also increased and sleepiness decreased in the young group, while the opposite was true of the older groups. The second study showed similar results, except that the temperature minimum of the young group was delayed about two hours while that of the older group was advanced by about one hour. Both studies clearly indicate that ageing reduces the ability to adapt to a new shift regimen.

1.2.2 Other disorders

1.2.2.1 Transmeridian flight

The world is becoming 'smaller', with bigger and faster jet aeroplanes allowing us to travel thousands of miles in a matter of hours, increasing the need for our bodies to become adjusted to a new environment as quickly as possible. However, the transition from one time zone to another results in a desynchrony between internal biological rhythms and the environment. Crossing one or two time zones is within the range of entrainment of the endogenous clock allowing rapid adjustment with few if any noticeable physiological effects. However, increasing the number of time zones travelled goes beyond the range of entrainment resulting in desynchrony. This desynchrony produces a number of complaints in the time zone traveller including insomnia, reduced efficiency and general discomfort (Siegel et al, 1969; Désir et al, 1981; Arendt and Marks, 1982; Arendt et al, 1987) and is often termed 'jet-lag'. Jet-lag problems are similar to those of shift work in some respects. However, after time
zone transition, travellers adapt with the help of local time cues, whereas shift workers are in conflict with local time cues.

A consistent finding in most studies on jet-lag is that there appears to be more circadian disruption following an eastward flight than a westward flight (Désir et al, 1981; Févre-Montange et al, 1983; Nicholson et al, 1986; Gander et al, 1989). Since travel in a westerly direction involves a phase delay and in an easterly direction involves a phase advance, the difference in adaptation rate is most likely due to the fact that the endogenous free-running period in humans is normally greater than 24 hours, and hence there is a natural tendency to phase delay.

The disruption of jet lag is of obvious importance to the business traveller, who needs to be fit and alert when arriving at a new time zone, and also for the holiday maker who does not wish to spend the first few days recovering from time zone transition.

1.2.2.2 Blindness

While many blind individuals report no problems of night time sleep or daytime alertness, some suffer from extensive insomnia and day time fatigue. The problems in these individuals have been attributed to the desynchrony between endogenous circadian rhythms and the environment (Miles et al, 1977; Orth et al, 1979; Sack et al, 1992a; Nakagawa et al, 1992a,b; Klein et al, 1993; Lockley et al, 1997b).

It is possible to group blind individuals according to their circadian rhythm patterns. Lewy and Newsome (1983) and Lockley et al (1997b) have shown three distinct groups according to the rhythm of melatonin secretion; a normally entrained group with patterns similar to normal sighted humans, an abnormally entrained group with 24 h patterns peaking at the same time but during the day and a free-running group with a melatonin rhythm running at the endogenous tau. Further work has shown that blind individuals with no light perception are more likely to be in the latter two groups than those with some perception of light (Lockley et al, 1997a). The importance of abnormal melatonin secretion in blind individuals is becoming more apparent, with new work showing a possible link between daytime peaks in melatonin and the increased propensity to nap (Lockley et al, 1997b).
The alternate insomnia and fatigue resulting from desynchronised circadian rhythms in blind individuals is of obvious importance given the impact it has on their normal social and work activities.

1.2.2.3 Psychiatry

The disorders commonly associated with biological rhythms are delayed and advanced sleep phase syndrome and seasonal affective disorder. The term 'delayed sleep phase syndrome' was first used by Weitzman et al (1981) to describe a disorder in insomnia patients. Sufferers of this disorder characteristically were unable to get to sleep at a socially accepted time, slept well when not on a strict schedule and hence delayed their sleep onset, and had a long history of unsuccessfully trying to treat the problem. It was hypothesised that this disorder arose in people with a PRC to light which had a much less prominent advance portion than delay, thus tending more to a delayed sleep onset (Weitzman et al, 1981). However, studies have since shown that the melatonin rhythms in people who suffer from this disorder have normal profiles (Dahlitz et al, 1991; Alvarez et al, 1992). Thus it appears that the problem exists as a dissociation of the sleep-wake cycle from normal endogenous rhythms. Advanced sleep phase syndrome shows the reverse characteristics and is much less common.

Seasonal affective disorder (SAD) was first described by Rosenthal et al (1984) as recurring episodes in autumn and winter of depression, hypersomnia, increased appetite (especially for carbohydrates) and weight gain, which were diminished by bright light treatment. The reason for the occurrence of SAD was considered to be due either to an abnormally phase delayed endogenous rhythm with respect to the sleep-wake or light-dark cycle (Lewy et al, 1988), or a diminished endogenous amplitude compared to unaffected individuals (Czeisler et al, 1987). Recent studies have showed that while the temperature rise of SAD patients was phase delayed compared to normal volunteers (Wirz-Justice et al, 1995), there was no difference in the amplitude, phase or duration of melatonin secretion (Checkley et al, 1993; Wirz-Justice et al, 1995). There is still no consensus as to the causes of SAD.
1.3 Potential treatment strategies

1.3.1 Artificial bright light

Suitably timed bright light of sufficient intensity and duration can phase shift biological rhythms, for example melatonin and temperature (Shanahan and Czeisler, 1991), according to a phase response curve (Czeisler et al, 1989; Minors et al, 1991; Van Cauter et al, 1994) as mentioned earlier. The potential for light treatment is well recognised in the circadian field, with research looking at treatment strategies for seasonal affective disorder (Lewy et al, 1986), delayed sleep phase syndrome (Rosenthal et al, 1990) and jet lag (Daan and Lewy, 1984). However, most research in this area has concentrated on the treatment of shift work rhythm disorders.

In many field based situations the timing of bright light exposure can often occur at the wrong part of the phase response curve, which results in a complete lack of phase shifting to adapt to night work (for example Roden et al, 1993). Indeed, adaptation in the complete absence of bright light has been shown in some workers (for example Midwinter and Arendt, 1991; Koller et al, 1994; Sack et al, 1992b, 1994), the lack of opposition to the phase shift being considered the main factor involved.

One of the most important concerns of night shift work is safety on the job. Several simulation studies have looked at the effect of light treatment on alertness and performance. Increases in cognitive performance and alertness during the night have been shown by French et al (1990), using 3000 lux light intensity throughout the night compared to 100 lux, Campbell and Dawson (1990), using 1000 lux on an 8 h simulated night shift compared to 10-20 lux and 100 lux, Czeisler et al (1990), using 7,000 - 12,000 lux overnight, and Daurat et al (1993), using >2000 lux compared to 150 lux throughout a 24 h constant routine (0900h - 0900h). Deacon and Arendt (1994) were able to phase delay the alertness rhythm, with a rhythm peak moving from the early afternoon to the late evening, by exposing subjects to a 1200 lux light pulse for six hours over three successive days. The pulse was initiated at 2000 h on the first day, 2200 h on the second day and 2400 h on the third day in order to enhance the natural tendency of circadian rhythms to delay.
Czeisler et al (1990) showed phase delays of the core body temperature and cortisol to the imposed regimen when light (7,000 -12,000 lux) was used between 0015 h and 0745 h (the delaying portion of the light PRC) and darkness was imposed during the day. Eastman (1992) found similar results when using a three to six hour light pulse (5000 lux) at various times during the night. Temperature was delayed or advanced, up to two hours per day, depending on the timing of the pulse according to the PRC for light. Deacon and Arendt (1994) reported a phase delay (> 2 hours) in the melatonin rhythm of volunteers on the protocol mentioned above. They succeeded in delaying the circadian system by nine hours using nine hours of light (1200 lux), followed by eight hours imposed darkness/sleep three hours later each day, with no deleterious effects on sleep, alertness or performance (Deacon and Arendt, 1996). A recent study by Ribeiro et al (submitted) now indicates that light may have acute affects on other hormones in the body, with the high levels of TAG resulting from a meal late at night being significantly lowered by light (1500 lux).

Field studies looking at the use of light treatment in shift work are considerably more difficult than simulation studies considering the conflicting factors involved and the expense of setting up the lighting regimen. However, several excellent studies have been produced giving much hope for more substantial use of light treatment in industry.

Field studies looking at subjects in Antarctica have shown that a skeleton photoperiod of bright full spectrum light (>2500 lux), given at 0800 h - 0900 h and 1600 h and 1700 h, significantly increases the rate of melatonin adaptation to day shift following night shift in the winter (Midwinter and Arendt, 1991). Further studies have indicated that dim red light (>500 lux) was more effective at facilitating readaptation to day shift than bright white light (2500 - 3000 lux) when administered between 1100 h and 1300 h (Ross et al, 1995). Eastman et al (1994) have shown that the phase shifting effects of light in shift work can be enhanced by light avoidance during the hours outside work. In their study they used bright (5,000 lux) or dim (<500 lux) light on night shift with or without dark goggles during the day. The combination of goggles plus bright light produced the maximum phase shift of the core body temperature rhythm, while the combination of dim light and no goggles
produced the least effect. Light treatment has been implemented for use in Space Shuttle missions, where 10,000 lux has been used to delay rhythms to specific shift schedules successfully in astronauts, who report improved sleep, performance and physical and emotional well-being (Stewart et al, 1995).

1.3.2 Exogenous melatonin

The use of exogenous melatonin in the alleviation of problems of jet lag and to facilitate adaptation of endogenous rhythms to new time zones has been extensively evaluated (Arendt et al, 1987; Arendt and Aldhous, 1988; Samel et al, 1991; Claustrat et al, 1992; Petri et al, 1993). Exogenous melatonin administration to blind individuals has been shown to be successful at reducing sleep problems and also modifies the melatonin rhythm (Arendt et al, 1988; Aldhous and Arendt, 1991; Tzischinsky et al, 1992). However, it remains unclear as to whether melatonin can fully entrain endogenous rhythms in free-running blind or sighted individuals (Folkard et al, 1990; Sack et al, 1987; Sack et al, 1991).

The main theoretical use of exogenous melatonin in shift work is for phase shifting circadian rhythms and reducing sleep problems. The exact mechanism of its actions is still unclear, but melatonin receptors have been found in the SCN (Reppert et al, 1988) suggesting that it may exert its effects directly on the biological clock. In general, melatonin is administered according to its phase response curve (Lewy et al, 1992) to promote either a phase advance or delay. Very few studies have, however, looked at the effects of melatonin in shift workers due to the expense of field studies and the lack of control over environmental zeitgebers.

Folkard et al (1993b) showed that administration of exogenous melatonin (5mg) taken at the desired bedtime, in police shift workers, improved the quality and duration of daytime sleep when on night shift. Night-time sleep was also improved with melatonin when the night shifts were finished. Calmness, cheerfulness and especially alertness were found to be improved after melatonin administration, and while memory scanning speed was reduced, five-target accuracy appeared to be improved.
Sack et al (1994) looked at the shift in melatonin onset, after a week of night shift, with and without exogenous melatonin. Most of the individuals had a phase shift of their melatonin rhythms, the average shift being about one hour per day. Some individuals also shifted under placebo treatment.

In both of the above studies melatonin was administered at the desired bedtime, corresponding to a phase-delay position on the melatonin PRC. Although this timing is good for the hypnotic effects of melatonin (Waldhauser et al, 1990), a more precise method of timing could be calculated from the melatonin PRC which would give maximum phase shifting ability in the direction (advance or delay) required.

1.3.3 Napping

Several studies have looked at the effect of naps at varying times on performance, alertness, mood and sleep characteristics. The relevance of this research can be seen especially in industry, where the benefits of prophylactic naps and potential hazards of napping ‘on the job’ can be of considerable importance. Before discussing the use of prophylactic naps as a treatment strategy however, it is important to note the level of napping and its effects in the normal work environment. Data on napping behaviour during work shifts can often be inaccurate depending on company policy and the type of operation undertaken. Workers who are allowed to nap during ‘quiet’ periods, for example ambulance crews, have no reason to falsify napping information. In companies where napping is not condoned, usually where continuous work or constant alertness are required, the information may not be so forthcoming due to fear of job loss. Two methods of assessing napping behaviour are questionnaires and EEG monitoring. While questionnaires could be considered to be the most inaccurate for data collection, the simple awareness of EEG monitoring can cause the subject to force wakefulness where napping would normally ensue. The following two studies used the two different methods for assessing nap behaviour. The first study, conducted by Åkerstedt and Torsvall (1985), looked at the napping behaviour questionnaires of 282 shift workers on a rotating three-shift system. The results showed that 49% did not nap on any shift, 18% napped on morning shift, 15%
napped on night shift and there was no napping on the afternoon shift. The napping behavior was closely related to the main sleep episode, compensating for sleep loss caused by the type of shift worked and diurnal type ('morningness' or 'eveningness' of the individual). The second study, by Torsvall et al (1989), looked at the napping behavior of 25 papermill workers during days of afternoon or night shift via 24-hour ambulatory EEG monitoring. As with the previous study, no napping occurred during the afternoon shift but 20% of the subjects showed incidents of sleep bouts during the night work. These naps ranged from 8 to 90 minutes in duration, were dominated by Stage 2 and SWS with no REM stage and mainly occurred during the second half of the night shift. Since sleep after night work was 2 hours shorter than after afternoon work, the researchers concluded that shift work disturbs both sleep and wakefulness to the extent where sleepiness during night work can reach a level where wakefulness cannot be maintained.

A series of studies by Bonnet have looked at the effects of prophylactic naps in constant routines with or without caffeine. One study, conducted on 104 young male adults, assessed the effects of prophylactic naps of various durations on performance, alertness and mood during 52 hours of continuous operation (Bonnet, 1991). Results supported a general dose response relationship between the length of prophylactic nap and measures of alertness, performance and mood. The effects lasted for the first 24 to 30 hours, after which the effects were eliminated. Further studies indicated that the combination of a prophylactic nap and caffeine (administered during the night) significantly improved objective and subjective alertness, performance on complex tasks, mood and increased oral temperature as compared to a prophylactic nap by itself (Bonnet and Arand, 1994a,b). It was suggested that the effect of caffeine might be either a function of its central stimulatory role or through a secondary increase in body temperature (Bonnet and Arand, 1994b). A study comparing the use of caffeine and prophylactic naps indicated that in general naps provided a longer and less graded change in alertness, performance and mood than caffeine, which had peak effectiveness and loss of effect within six hours (Bonnet et al, 1995).
In contrast to the simulated studies by Bonnet, field studies looking at the effect of napping at home on workers, at a nuclear power plant and a gas utility plant, found that greater sleepiness and diminished performance on some tasks were observed during the work shift on nap days compared to no-nap days (Rosa, 1993b). Napping was common in the shift workers, with more napping on the first day of shift than all the others combined, and occurred mainly in association with the night shift. Naps were considered to supplement the main period of sleep on the first workday and compensate for reduced sleep during the rest of the work week.

Napping during night work has been shown to be of benefit for shift workers who do not wish to adapt to the shift, such as those on short rotation where only 2 or 3 days are spent on night shift. Both Motohashi and Takano (1993), and Matsumoto and Harada (1994) have shown that napping during night work can prevent phase shifting of internal circadian rhythms. Matsumoto and Harada (1994) believe that the reduced fatigue and drowsiness observed during the recovery period, in shift workers who napped throughout night shift, may be due to the ‘anchor effect’ of the naps. This effect, described by Minors and Waterhouse (1981), is due to napping causing a sudden drop in body temperature and pulse rate, thus minimising the disruption to the circadian system.

1.3.4 Exercise/activity

Very little work has been done on the effect of exercise on human circadian rhythms. It has been shown that while afternoon exercise may help improve subsequent sleep quality, evening exercise may have an adverse effect (Desjardins et al, 1974). Could this then be interpreted as an anchor effect of afternoon exercise where high activity is expected, and/or a possible entraining effect of evening exercise where increased arousal leads to reduced sleep quality.

One of the main problems with assessing the phase shifting ability of exercise is that it has a very large masking effect on core body temperature, making that parameter difficult and unreliable to use. A study by Eastman et al (1995) looked at the effect of exercise on 8 normal subjects during a simulated night shift, compared with 8 control subjects. The temperature data collected had to be treated with
demasking formulae using baseline data, so the results must be considered with some caution. They found a larger temperature rhythm phase shift for the exercise group (6.6 ± 2.5 h, mean ± SD) than the control group (4.2 ± 3.4 h, mean ± SD) during the last 4 days of night shift compared to the last 5 days of baseline.

Other circadian rhythm markers, such as melatonin or cortisol, are considered more appropriate when looking at exercise and biological rhythms, due to a markedly reduced masking effect. A study by Theron et al (1984) has shown, however, that there are direct effects of exercise on these hormones, with significantly higher plasma melatonin, cortisol and prolactin levels during exercise than normal. Two studies looking at melatonin and thyroid stimulating hormone (TSH) rhythms have revealed a phase shifting effect of nocturnal exercise (Van Cauter et al, 1993; Van Reeth et al, 1994), with significant phase delays reported compared to baseline.

1.4 Rationale

Field studies, looking at the adaptation of the melatonin rhythms of shift workers to night shift have produced conflicting results (see section 1.2.1.1). While some studies have shown shifts in the phase position of melatonin to varying degrees, others have found no shift at all. One of the main complicating factors of such studies is that individuals often go home at the end of their work shift, resulting in exposure to a variety of influences such as natural light and family/social interaction. The regimen of an offshore oil installation was considered an excellent environment to study both the biological and psychological effects of shift work without such complications.

The primary aim of this work was to study the effects of night shift work on specific biological (melatonin) and psychological (sleep and alertness) parameters of the oil rig workers. With their avoidance of natural light during the night shift (1800h to 0600h) in winter, it was hypothesised that adaptation may be seen during this period but not in the summer, when natural light would be present throughout most of the night shift work period. Therefore, a study was conducted to assess the adaptive state of the workers during the winter and summer, and thus give a baseline set of data from which to build further studies. Within the winter study, two distinct groups of
work crews were studied; a crew with a very high physical workload (drillers) and a crew with much lighter monitoring work (maintenance technicians/engineers). It was hypothesised that the higher levels of activity found in the drill crew might have an effect on the adaptive state of that crew to night shift.

The possibility that adaptation to night shift may be dependent to some degree on the timing of the shift was a further consideration. Therefore a second study was conducted to look at the adaptation in a ‘swing’ shift system, where subjects underwent a week of what could be considered day shift work (1200h to 0000h), immediately followed by a rapid rotation to a week of night shift work (0000h to 1200h). Again, the study was run twice, once in the winter and once in the spring, to assess any seasonal effects.

The mechanism by which shift work leads to an increase in coronary heart disease (see section 1.2.1.6) is still unclear, but there is increasing evidence that it is the response to meals at times out of phase with the body clock that may promote risk factors. If this proves to be correct then not only will problems arise at the start of a night shift, but also at the end of night shift when changing back to a normal routine (or day shift) if full adaptation has occurred. To test the hypothesis that night shift leads to impaired post-prandial hormone and metabolic responses, a third study was conducted to assess these responses during a simulated night shift. The simulation was designed to match the first day on an offshore oil installation during day shift and night shift, under the regimen studied in the first baseline study. The use of bright light treatment throughout a second simulated night shift work period was designed to assess any change in hormonal responses under this condition (see section 1.3.1).

The final aim of this work was to assess the ability of exogenous melatonin treatment to facilitate readaptation back into a normal day-active pattern following night shift. It was hypothesised that the improvements in sleep parameters and potential phase shifting of the endogenous melatonin rhythm, observed by others (see section 1.1.3.2), under melatonin treatment would be reproduced when the workers returned home following a two-week night shift.
CHAPTER 2

MATERIALS & METHODS
2. Materials and Methods

The methods presented below describe the general approaches used to collect and analyse data. Specific methods which deviate from those below are described in the relevant sections of the results chapters that follow.

2.1 Subject criteria

All the studies involved healthy volunteers under no medication except for minor analgesics. Protocols for each study were approved by the University of Surrey’s Advisory Committee on Ethics (USACE). All subjects gave informed consent. Due to the lack of any female volunteers on the oil installations, only male volunteers were used for the simulation study. The exclusion criteria were as follows:

1) Subjects who had undertaken transmeridian flight in the two weeks prior to each study.
2) Familial or personal history of psychiatric disorders, sleep disorders, migraine or epilepsy.
3) In the case of the simulation study, subjects who donated blood within the preceding 4 months.
4) In the case of the melatonin study, subjects unable to provide written consent from their general practitioner.

2.2 Shift working groups

Two types of shift worker were assessed in the baseline studies; members of the drill crew and members of the operations technicians crew.

2.2.1 Drill crew

The drill crew are in charge of drilling wells, inserting pipe and removing pipe. Piping is generally stored on the pipe deck, where it is winched to the drill floor when needed. In order to insert piping into a well, a new section of pipe is first placed in a mechanical winch which has a top-drive motor capable of gripping and rotating large amounts of pipe. The winch raises the pipe level with a second one already in the well. The pipe is then manually directed onto the second pipe and
screwed on using the top-drive motor. The second pipe is prevented from rotating by a large metal grip, known as an iron 'roughneck'. The method of removing pipe is identical but in reverse.

The drill crew normally consists of a tool pusher, a driller, an assistant driller, a derrick man, several roughnecks and several roustabouts. The tool pusher is the head supervisor of the drilling operations and does no manual work. The driller and assistant driller operate the heavy winch that is used to lower and pull up piping from the well. The assistant driller also helps out on the drill floor when necessary. The derrick man spends much of his time working with the roughnecks or roustabouts, but his main purpose is to climb up the derrick (tower on which the winch is supported) and position the tops of the pipes for the winch or storage when necessary. The roughnecks spend all their time on the drill floor adding and removing pipes from the well (see Figure 2-1). The roustabouts work out on the pipe deck removing pipes and machinery from storage and winching them to the drill floor, or winching the same from the drill floor to the deck for storage (see Figure 2-2). Both the roustabouts and roughnecks tend to swap jobs back and forth. The baseline studies therefore concentrated on these two groups of shift workers within the drill crew.

Figure 2-1. Roughnecks working on the drill floor.

(a) Positioning pipe  
(b) Connecting two pipes
2.2.2 Operations technicians crew

This crew monitors and maintains most of the machinery on the installations except that connected with the drill floor. Such machinery includes pumps for water and oil, heaters, turbines and so on. Most of the crew are assigned particular projects which they take care of. A small subsection of the crew work in the control room, monitoring and adjusting equipment remotely. While these particular crew members spend most of their time in the control room, they also manually monitor equipment outside at various occasions during their shift.

2.3 Shift regimen

All the oil installations were located in the North Sea at 61°N (see Figure 2-3). Transport to the rigs was normally from Aberdeen to Sumburgh (Shetland Islands) by aeroplane and then on to the rigs by helicopter. Total flight time was approximately three hours, with a wait in Sumburgh of between half an hour and three hours.
2.3.1 Fixed oil platforms

These platforms have a rotating pattern of two weeks day shift, followed by two weeks leave, then two weeks night shift followed by another two weeks leave. In the case of the volunteers studied, day shift was from 0600h to 1800h and night shift was from 1800h to 0600h. Figure 2-4 shows the shift patterns.

2.3.2 Semi-submergible drilling platform

This rig also had a rotation of two weeks on and two weeks off, but the two weeks on consisted of one week of day shift (1200h to 0000h) followed by one week of night shift (0000h - 1200h). The two shifts were separated by a rapid rotation day with a work shift of 0800h to 1600h. Figure 2-5 shows the shift pattern.
Figure 2-4. Day and night shift patterns for the fixed oil platforms.

The stripped bars represent time off the installation, the black bars represent free time/sleep periods and the white bars represent the work shift.

Figure 2-5. Shift pattern for the drilling platform.

The stripped bars represent time off the installation, the black bars represent free time/sleep periods and the white bars represent the work shift.

2.4 Light intensity measurement

Light intensity was measured in both the baseline and nutrition studies. It could not, however, be measured in the melatonin study because the subjects were in
their individual homes. A standard digital lux meter (Full Spectrum Lighting, High Wycombe, Buckinghamshire, UK) was used with the sensor placed at eye level.

In the case of the baseline study the light intensity measurements were conducted for one day of each shift both in the summer and winter. Due to safety restrictions on the oil installations, the measurements were only done at the start and middle of the work period. Measurements were made at each site frequented by the subjects and throughout the accommodation area, facing the general directions that the workers themselves faced. The range and average levels for both the accommodation and work areas were calculated from recorded values.

Measurements for the nutrition study were recorded hourly throughout the awake periods on the study days. The sensor was placed in front of each subject's eyes facing forward, left and right. Readings were averaged over each period.

2.5 Collection and storage of samples

2.5.1 Urine

Urine was collected sequentially over 24 hour periods every 3 hours (with just one collection over the sleep period) for the duration of the baseline and nutrition studies, and for all non-treatment and non-washout days of the melatonin study. The subjects were allowed to urinate in between collection periods, but this was collected in the bottles provided and the total for that period was measured. For the baseline study, the investigator measured and recorded the total volume of each sample and aliquoted 2 ml samples which were immediately frozen (-20°C) without preservative. Stability studies have shown that aMT6s is stable in urine for up to five days at room temperature or 4°C, and for up to two years at -20°C with or without preservative (Bojkowski, 1988). For the remaining studies the subjects measured, recorded and aliquoted the samples themselves before freezing.

2.5.2 Blood plasma

Blood plasma was only collected for the nutrition study. An indwelling canula was placed into an antecubital vein of each subject prior to the test meal. Two baseline samples were taken at 10 and 0 minutes before the test meal and then further samples were taken at 15, 30, 45, 60, 75, 90, 120, 150, 180, 240, 270, 300 and 360
minutes thereafter. 12 ml of blood were taken at each time point and centrifuged at 3000rpm for 10 minutes. The plasma was removed immediately and aliquoted into four tubes containing lithium/heparin, fluoride oxalate and two separate EDTAs for glucose, insulin, TAG and NEFA analysis respectively. The samples were immediately stored at -20°C.

2.6 Radioimmunoassay

2.6.1 Basic principle

Both radioimmunoassays used involve the competition between labelled and unlabelled antigen to give a quantitative value. A sample, containing the unlabelled antigen to be tested, is added to a fixed amount of antiserum specific to that antigen. A fixed amount of radiolabelled antigen is then added, resulting in a competition for the limited number of antibody binding sites. Since the amount of labelled antigen and antibody binding sites are constant, the amount of radioactivity associated with the antibody depends on the concentration of antigen in the sample. After allowing a suitable period of time to reach equilibrium, the free and bound fractions of the antigen can be separated by charcoal (in the case of aMT6s), or with a second precipitating antibody system (in the case of insulin). Therefore, using a set of standards of known concentrations, the antigen concentration in the sample can be measured by comparing the amount of radioactivity in either the bound or free fractions.

2.6.2 aMT6s

Urinary 6-sulphatoxymelatonin was measured by specific radioimmunoassay using an iodinated tracer (Aldhous et al. 1988). Diluted samples were incubated with a specific antiserum to aMT6s followed by trace amounts of iodinated aMT6s. The free and antibody-bound fractions of aMT6s were separated using a dextran-coated charcoal suspension. The free aMT6s fraction was precipitated with the charcoal by centrifugation and the radioactivity counted on a gamma counter. A standard curve was constructed at the same time and used to calculate the concentration of the aMT6s in each sample.
2.6.2.1 Materials

All water used was freshly double-glass distilled water (DGDW) and stored in glass.

- Buffer (pH 5.5): 17.9g tricine (Sigma Ltd. product no. T-0377) + 0.9g NaCl + 1.0g gelatin made up to 1 litre with DGDW.

- Antiserum: Sheep anti-aMT6s antiserum (batch number G/S/1118-23884) supplied freeze dried (Stockgrand Ltd. product no. AB/S/04) and reconstituted with 1ml DGDW and 9ml assay buffer. The working dilution of 1:20,000 was made up by diluting a 100μl aliquot with 20ml assay buffer, sufficient for 100 assay tubes. The lower limit of sensitivity is 1pg/tube.

- Dextran-coated charcoal: Activated charcoal (Sigma Ltd. product no. C-5260) suspended in assay buffer at 2% w/v with dextran T-70 (Sigma Ltd. product no. D-1390) at 0.02% w/v. It was stored for no longer than one week at 4°C.

- Radiolabel: Iodinated aMT6s (125I-aMT6s) was made in house by a method adapted by Vakkuri et al (1984). The average yield is 100μCi in the specific 125I-aMT6s fraction and the radiolabel can be stored for up to 4 months at 4°C. The working solution was prepared by diluting the stock solution with assay buffer to give 8,000 to 10,000 cpm/100μl and was freshly made for each assay.

- Charcoal stripped urine (CSU): This was made in-house and supplied freeze dried (100μl per vial), aMT6s free. It was stored at -20°C and reconstituted with 25ml assay buffer to give a working dilution of 1:250.

- Standards: 500pg aMT6s used for one standard curve at 200pg/ml in 1:250 diluted CSU. The standard curve was produced from further dilution in CSU to provide standards 0, 1, 2, 4, 8, 14, 20, 40 and 100pg.

- Quality control samples (QCs): Low, medium and high urine samples provided at 3.5, 23 and 45 ng/ml respectively. Diluted 1:250 with assay buffer prior to assay using an automatic diluter.

- Urine samples: Samples were diluted identically to the quality controls. Samples which were too concentrated (> 50 ng/ml) or too dilute (< the calculated detection limit) were diluted 1:500 or 1:125 respectively instead of 1:250 prior to assay.
2.6.2.2 Method
The assay was carried out at room temperature unless otherwise stated. All tubes were done in duplicate.
1. Standards and diluted CSU were pipetted to form the standard curve (500µl per assay tube in duplicate). 500µl of CSU was also added to the non-specific binding (NSB) tubes.
2. 500µl of diluted urine sample was pipetted into assay tubes in duplicate. The quality control samples were treated identically to the samples.
3. 200µl of diluted antiserum was added to all tubes except for the total count and NSB tubes. 200µl of buffer was added to the NSB tubes instead of antiserum. The tubes were vortexed and incubated at room temperature for 30 minutes.
4. 100µl of radiolabel was added to all tubes. Tubes were vortexed and incubated for 15-18 hours at 4°C.
5. 100µl of dextran-coated charcoal was added to all tubes except total count tubes and vortexed.
6. All tubes except total count tubes were centrifuged at 3500 rpm at 4°C for 15 minutes.
7. Supernatant was decanted and discarded and the tops of the tubes were blotted dry.
8. All tubes were then counted in a gamma-radiation counter (Wallac 1470), for 1 minute each, in the following order:

   Total counts
   NSBs
   Standard curve
   QC  s
   Samples
   QC  s

   The aMT6s concentration in the samples was automatically calculated from the dose response curve using Multicalc Level 4.M software (Wallac, Turku, Finland). Cosinor analysis was then performed on the data.

Sensitivity: Based on twice the standard deviation from zero binding is 0.5 ng/ml.
2.6.3 Insulin

The method used was developed in-house by Dr S. M. Hampton (Hampton et al, 1983). Antibodies against insulin were raised from guinea pigs immunised with porcine insulin. Separation of the assay occurred using a second antibody (donkey anti-guinea pig) by a double antibody plus polyethylene glycol method.

2.6.3.1 Materials

Freshly made double deionised water was used to prepare all the reagents and was stored in glass on the day of use.

- Buffer (pH 7.4): 23g Na₂HPO₄ anhydrous salt + 5.97g NaH₂PO₄·2H₂O made up to 5L followed by addition of 0.5% bovine serum albumin (BSA).
- Charcoal stripped serum (CSS): This was made in-house, supplied in 10ml aliquots frozen at -20°C, insulin free and used directly without dilution.
- Insulin antiserum: Batch number MF/GP/2 VILA. Raised in a guinea pig injected with porcine insulin conjugated to egg albumin and diluted 1:1000 before use.
- Radiolabel: Made in house and donated by Dr. S. M. Hampton. The working solution was prepared by diluting the stock solution with assay buffer to give 8,000 to 10,000 cpm/100μl and was freshly made for each assay.
- Standard: Supplied by the National Institute of Biological Standards and Controls. Diluted in buffer and stored freeze dried. Reconstituted in 0.1ml double deionised water and 0.9ml buffer to provide the top standard of 1500pmol/L (200mU/L) then double diluted with buffer to produce standards containing 750, 375, 187, 94, 47 and 23pmol/L.
- Second antiserum (Dab): Donkey anti-guinea pig diluted 1:16 in buffer prior to use.
- Normal guinea-pig serum (NGPS): Diluted 1:200 in buffer prior to use.
- Polyethylene glycol 6000 (PEG): A 4% solution made up in buffer.
- Quality controls: A low, medium and high serum quality control, used directly in the assay without prior dilution.
- Samples: Defrosted and re-frozen on the day of assay. Treated identically to quality controls.
2.6.3.2 Method
The assay was carried out on an ice tray unless otherwise stated. All tubes were done in duplicate.

1. Standards and diluted CSS were pipetted to form the standard curve (400μl per assay tube in duplicate). 50μl of CSS and 250μl of buffer were added to the zero tubes of the standard curve. 50μl of CSS and 350μl of buffer were also added to the reagent non-specific binding (NSB) tubes.

2. 50μl of sample and 250μl of buffer were pipetted into assay tubes in duplicate. 50μl of sample (one random per subject in duplicate) and 350μl of buffer were also pipetted into test serum NSB tubes. The quality control samples were treated identically to samples.

3. 100μl of antiserum was added to all tubes except for the total count tubes and the NSB tubes.

4. 100μl of radiolabel was added to all tubes. Tubes were then vortex mixed and incubated for 24 hours at 4°C.

5. 100μl of NGPS, 100μl of Dab and 700μl of 4% PEG was added to all tubes except the total count tubes, vortex mixed and incubated for 2 hours at 4°C.

6. All tubes except total count tubes were centrifuged at 2500 rpm at 4°C for 30 minutes.

7. Supernatant was aspirated from all tubes except the total count tubes and discarded.

8. All tubes were counted in a gamma-radiation counter (Wallac 1470) for 2 minutes each in the following order:

   Total counts
   Reagent NSBs
   Standard curve
   QCs
   Test serum NSBs
   Samples
   QCs

The insulin concentration in the samples was automatically calculated from the dose response curve using WIACALC.
Sensitivity: Based on twice the standard deviation from zero binding is 16 pmol/L.
Specificity: Crossreactivities at 50% displacement of tracer.

<table>
<thead>
<tr>
<th>% Crossreactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Biosynthetic Insulin</td>
</tr>
<tr>
<td>Human Biosynthetic Proinsulin</td>
</tr>
<tr>
<td>Des 64-65 Biosynthetic Proinsulin</td>
</tr>
<tr>
<td>Des 31-32 Biosynthetic Proinsulin</td>
</tr>
</tbody>
</table>

2.7 Spectrophotometry

2.7.1 Glucose

Plasma glucose was measured by an enzymatic UV test, using the enzymes hexokinase (HK) and glucose-6-phosphate dehydrogenase (G6P-DH), on an automated enzymatic spectrophotometer (Cobas Mira Plus, Roche Diagnostics Ltd., Welwyn Garden City, Hertfordshire, UK). The principle reactions that occurred were as follows:

\[ \text{D-Glucose} + \text{ATP} \overset{\text{HK}}{\longrightarrow} \text{D-glucose-6-P} + \text{ADP} \]

\[ \text{D-Glucose-6-P} + \text{NAD}^{+} \overset{\text{G6P-DH}}{\longrightarrow} \text{D-gluconate-6-P} + \text{NADH} + \text{H}^{+} \]

The formation of NADH is directly related to the glucose concentration and is measured photometrically.

2.7.1.1 Materials

- Glucose HK kit (art. 07 3672 4, Roche Diagnostics Ltd., Welwyn Garden City, Hertfordshire, UK). Provides all the reagents for the assay in two separate reagent mixtures; R1 and R2.
  R1 contents: TRIS (85 mmol/L), ATP (3.6 mmol/L), NAD (1.8 mmol/L), HK (≥20 μkat/L) and G6P-DH (≥10 μkat/L).
  R2 contents: TRIS (10 mmol/L) and sodium azide (<0.1%).
- Quality controls: Roche Control Serum N (art. 07 3711 9) and Roche Control Serum P (art. 07 3712 7). Both provided with the kit.
- Samples: Defrosted on day of use. Used directly in the assay without prior dilution.
2.7.1.2 Method

The assay was carried out at room temperature.

1. Reagent R1 reconstituted with 30ml of R2 to produce the working reagent which
   was inserted into the Cobas.

2. Samples and QCs were pipetted into the Cobas cells (70μl per cell).

3. The Cobas then mixed 4μl of sample/QC with 200μl of working reagent, in a
cuvette with a 1cm light path, and incubated for 10 minutes.

4. Absorbance was measured at 340 nm and the concentration of glucose was
calculated automatically.

2.7.2 TAG

Plasma TAG was measured by an enzymatic colourimetric test, using the
enzymes lipase, glycerol kinase (GK) and glycerol phosphate oxidase (GPO), on an
automated enzymatic spectrophotometer (Cobas-Mira). The principle reactions that
occurred were as follows:

\[
\text{Triglyceride} \xrightarrow{\text{lipase}} \text{glycerol} + \text{fatty acids}
\]

\[
\text{Glycerol} + \text{ATP} \xrightleftharpoons{\text{GK}} \text{glycerol-3-P} + \text{ADP}
\]

\[
\text{Glycerol-3-P} + \text{O}_2 \xrightarrow{\text{GPO}} \text{dihydroxyacetone phosphate} + \text{H}_2\text{O}_2
\]

In the presence of peroxidase the hydrogen peroxide (\(\text{H}_2\text{O}_2\)) formed effects the
oxidative coupling of 4-chlorophenol and 4-aminoantipyrine to form a red-coloured
quinoneimine derivative. The colour intensity is directly related to the TAG
concentration and is measured photometrically.

2.7.2.1 Materials

- Triglyceride kit (art. 07 3679 1, Roche Diagnostics Ltd., Welwyn Gar den City,
  Hertfordshire, UK): Vial R - Provides the reagents for the assay.
  Contains: PIPES buffer pH 7.5 (42mmol/L), ATP (1mmol/L), 4-aminoantipyrine
  (0.5mmol/L), lipoprotein lipase (≥ 50μkat/L), GK (≥ 13μkat/L), GPO (≥
  25μkat/L), peroxidase (≥ 5μkat/L) and 4-chlorophenol (6mmol/L).
- Quality control: Roche Lipid Control Serum (art. 07 3719 4).
- DGDW: Made fresh on the day of assay.
- Samples: Defrosted on day of use. Used directly in the assay without prior
dilution.
2.7.2.2 Method

1. Contents of vial R were reconstituted with 30ml DGDW to produce the working reagent which was inserted into the Cobas.

2. Samples and QC were pipetted into the Cobas cells (70µl per cell).

3. The Cobas then mixed 4µl of sample/QC with 300µl of working reagent, in a cuvette with a 1cm light path, and incubated for 20 minutes at 25°C.

4. Absorbance was measured at 500 nm and the concentration of TAG was calculated automatically.

2.7.3 NEFA

NEFA was measured in plasma by an enzymatic colourimetric test on an automated spectrophotometer. The reaction occurred in three steps. Firstly coenzyme A was acylated by NEFA when acyl-CoA synthetase was added. The acyl-CoA produced was then oxidised by the addition of acyl-CoA oxidase resulting in the formation of hydrogen peroxide. In the presence of peroxidase the hydrogen peroxide facilitated the oxidative condensation of 3-methyl-N-ethyl-N-(β-hydroxyethyl)-aniline with 4-aminoantipyrine resulting in a purple adduct which was measured colourimetrically at 550nm.

2.7.3.1 Materials

All reagents necessary for the test were provided in a NEFA C kit (code no. 99475409 E) from Wako Chemicals USA, Inc. (Richmond, USA). The contents of the kit were as follows:

- Colour reagent A - Acyl-coenzyme A synthetase (3 U/vial), ascorbate oxidase (30 U/vial), coenzyme A (7 mg/vial), ATP (30 mg/vial) and 4-aminoantipyrine (3 mg/vial).

- Solvent A - Phosphate buffer (pH 6.9, 0.05 mol/L), magnesium chloride (3 mmol/L), surfactant and stabilisers.

- Colour reagent B - Acyl-coenzyme A oxidase (132 U/vial) and peroxidase (150 U/vial).

- Solvent B - 3-methyl-N-ethyl-N-(β-hydroxyethyl)-aniline (1.2 mmol/L) and surfactant.

- NEFA standard solution - Oleic acid (1.0 mmol/L), surfactant and stabilisers.
2.7.3.2 Method

The assay was carried out at room temperature.
1. Colour reagent A was reconstituted with 10ml solvent A to produce colour reagent A solution and inserted into the Cobas. Colour reagent B was reconstituted with 7.5ml solvent B to produce colour reagent B solution and inserted into the Cobas.
2. Standard, samples and QC were pipetted into the Cobas cells (70μl per cell).
3. The Cobas then mixed 50μl of standard/sample/QC with 1ml colour reagent A in the cuvette with a 1cm light path and incubated for 10 minutes at 37°C.
4. The Cobas then added 2ml colour reagent B in the cuvette and incubated for 10 minutes at 37°C.
5. Absorbance was measured at 550 nm and the concentration of NEFA was calculated automatically.

2.8 Behavioural measurements

2.8.1 Subjective sleep logs

Sleep logs were completed daily by all the subjects in each study. The log was designed by the investigator, but originally developed by Prof. A. Borbély (University of Zurich, Switzerland), and is shown in Figure 2-6. The last two questions of the log were answered on visual analogue scales (VAS) which comprised a 10 cm long horizontal line. The subjects marked the VAS at a position relative to how they felt and the response was then scored out of ten by measurement along the line. The following parameters were extracted from the data:
1) Sleep latency - the time taken to fall asleep.
2) Sleep duration - time of waking up (sleep offset) minus time of starting to sleep (sleep onset) minus the length of any awakenings.
3) Sleep efficiency - the percentage of time spent actually asleep, from the time of trying to sleep to sleep offset.
4) Sleep quality - assessed on VAS.
In an attempt to remove the effects of interindividual differences in sleep patterns and subjective sleep measurement, the raw data for each parameter were initially treated by expressing values as percentages of shift means. However, values were often higher than the shift mean, resulting in treated data that were over one hundred percent. Consequently the treatment method was changed to express values as plus or minus individual shift means. This was done by subtracting an individual's shift mean from his raw values. The shift mean of each individual thus became equal to zero and values were expressed as plus or minus this point. Day of study effects within each shift were assessed by one-way ANOVA with Duncan's New Multiple Range post-hoc testing, using treated data from all subjects in a group. Day by day
differences between shifts were compared by Student's t test using treated data only from subjects that completed both shifts.

Comparisons between day shift and night shift for each group were initially assessed by repeated measures ANOVA of treated data from individuals who completed both shifts. However, following a deeper understanding of this particular statistical method it was realised that raw data should be used instead because each individual within a group was only compared with their own data. Individual differences between shifts were assessed by one-way ANOVA of raw data.

For the baseline studies, the sleep parameters were also related to the phase of the aMT6s rhythm by plotting a scattergraph of treated sleep data against aMT6s acrophase relative to each individual's day shift mean (calculated by subtracting the day shift mean from each night shift acrophase). For subjects who did not take part in a day shift study, the group average day shift acrophase was used to treat the data. The scattergraph was used to plot a linear regression line through the data, and the resulting $r$ value was used with the degrees of freedom to calculate the level of significance from a Product-Moment Correlation Coefficient table.

2.8.2 Actigraphy

2.8.2.1 Monitoring

The activity monitor used in the two baseline studies conducted on the fixed oil platforms was the MINI Motionlogger (Ambulatory Monitoring Inc., New York, USA), while that used on the remaining studies was the Actiwatch AW3 (Cambridge Neurotechnology, Cambridge, UK). Both utilised an accelerometer to monitor the occurrence and degree of motion. The accelerometer is bar shaped and flexes when the monitor is moved. The degree and force of the flexing produces a voltage in the sensor that corresponds to a number of activity counts (maximum sampling frequency of 10 Hz and 32 Hz for the MINI Motionlogger and Actiwatch respectively). The sensor is sensitive to motion in all three axes of movement (omnidirectional).

The MINI Motionlogger required downloading to a computer every seven days due to memory restrictions. The Actiwatch was capable of lasting 21 days before downloading. These durations were based on one-minute epoch recordings, where the activity monitor recorded the amount of movement per minute.
Downloading was via an interface plugged into the serial port of an IBM compatible computer.

The wrist activity monitors were worn by the subjects, on their non-dominant wrists, throughout each study except when washing, bathing or showering. In this way activity was monitored both during the subjective day and the sleep period. However, the strict work regimen on the oil installations meant that activity was relatively constant on the work shift. Therefore the actigraphy analysis concentrated on the sleep period. Studies looking at automatic sleep scoring from actigraphic data have shown good correlation with EEG recordings (Cole et al, 1992). Lockley et al (1999) have also shown a good comparison between actigraphic and subjective sleep. Hence this method, together with subjective sleep records, was deemed suitable for sleep analysis.

2.8.2.2 Analysis

Two computer programs were used for the actigraphic sleep analysis; Action 3 (Ambulatory Monitoring Inc.) for the MINI Motionlogger and Sleep Watch v2.42 (Cambridge Neurotechnology Ltd.) for the Actiwatch. In both programs, sleep was analysed by manual entry of the bedtime and wake up times from subjective sleep records. The programs then calculated objective parameters of sleep onset and offset, sleep latency, number and length of awakenings, total number of minutes asleep, total number of minutes awake and sleep efficiency (percentage of time actually spent asleep between sleep onset and offset).

The data were then analysed as in Section 2.8.1. Comparisons between subjective and actigraphic sleep were assessed by repeated measures ANOVA of raw data only from individuals who completed both forms of sleep recording.

2.8.3 Subjective alertness

All the subjects in each study apart from the simulation study were asked to complete subjective alertness assessment at the same time as each urine collection. The assessment consisted of one VAS of 10 cm in length, with a rating of 'very alert' on one side and 'very drowsy' on the other. The assessments were scored out of ten by measuring the distance from the 'very drowsy' end of the line to the subjects' marks.
Computerised cosinor analysis was the initial method of choice for analysing alertness because data were entered rapidly into the computer program and fitted to a cosine curve, resulting in the calculation of daily rhythm peak (acrophase) and amplitude. However, the method was reliant on a large number of fairly evenly distributed data points per day. Given the nature of the work offshore it was considered necessary to develop a second method of analysis, which would require less data points to still give a meaningful result. Therefore the area under each alertness curve throughout the work period was calculated by summation of the area under the curves (AUC) for the first and second halves of each work shift. Each AUC was calculated by plotting the alertness data using a line fit, reading off the alertness levels at 0, 6 and 12 hours after the work shift began, and then calculating the area of the trapezium in each six hour segment. The lines were not extrapolated over sleep periods and consequently the total AUC could not be calculated on days where there were a lack of data points around the start or end of the work shift. The resulting data were used for further statistical analysis as in section 2.8.1.

2.8.4 Performance tests

The tests were done every hour on Psion series II LZ hand held computers for the simulation study only. Each set of tests took approximately 45 minutes to complete and the subjects were then allowed a 15 minute break. The main use of the tests was to simulate the levels of concentration required by control room operators in the field. For each measurement, overall comparisons between shifts were achieved by repeated measures ANOVA, while comparisons between shifts for each time point were assessed by paired t-tests. Overall within shift differences between time points were achieved by one-way ANOVA, with Duncan's New Multiple Range post-hoc testing to indicate significant differences between specific days. The statistical analysis was done on raw data, but the resulting graphical plots were done using treated data, as described above, to allow some clarity for inspection. The list of tests, developed by Totterdell and Folkard (1992), their descriptions are given below.

2.8.4.1 Serial choice reaction time

This test consisted of two blocks of 80 stimuli. Subjects were required to press either M, T, W or R on the keypad depending on the position of an asterisk in
the display. The keys were chosen for finger positions; M and T for the left hand, W and R for the right hand. As soon as the subject made a response the next asterisk would appear. For each hand the following data were recorded:

- mean response time in hundredths of a second
- mean response time for correct responses
- mean response time for incorrect responses
- % trials incorrect
- % trials above threshold

2.8.4.2 Sternberg memory search test

In this test the subjects had to memorise five letters. A string of 40 letters (probes) were then displayed one at a time and the subject had to press T if one of the memorised letters appeared or F otherwise. Both the list of letters to be memorised and the probe letters were random from the alphabet excluding vowels and the letters T and F. Each probe had an equal probability of having been or not been in the list. The probes followed on from each other immediately. The next probe was displayed after five seconds if the subject failed to respond. The following data were recorded:

- presentation time of the list in seconds
- number of true positives
- mean response to true positives in hundredths of a second
- number of false positives
- mean response time to false positives
- number of true negatives
- mean response time to true negatives
- number of false negatives
- mean response time to false negatives
- number of trials on which subject failed to respond

2.8.4.3 Alertness, cheerfulness and calmness

Unlike the baseline or melatonin studies, the availability of Psion computers in this study allowed easy measurement of alertness, cheerfulness and calmness immediately before the performance tests. Each measurement was done on a visual
analogue scale twenty units in length, with zero being the lowest level and twenty being the highest. Statistical analysis was carried out as in section 2.8.1.

2.8.5 Shift work questionnaire

This was completed once by each subject in the baseline studies and can be found at the end of Appendix I. The questionnaire was based on The Shiftwork Survey (The Shiftwork Research Team, MRC/ESRC Social and Applied Psychology Unit, Sheffield University) with an additional section on nutrition (developed by Dr. J. Lovegrove, Reading University). The questions asked related to the effects of shift working on life at work and when at home on leave. The purpose of the survey was to provide a source of information to help explain any anomalous sleep, alertness or urinary data.

2.9 Analysis of physiological data

2.9.1 aMT6s data

Cosinor analysis was used to assess the rhythmic production of aMT6s. A computer program, developed by Dr. D. S. Minors (Manchester University), attempted to fit the manually entered rates of production to a cosine curve. The period of the rhythm was assumed to be 24 hours, since the subjects were exposed to a daily routine, albeit reversed on night shift. The resulting daily rhythm curves facilitated assessment of acrophase (rhythm peak), amplitude (variation in concentration over time) and mesor (mean concentration over time). The program did however assume that the rhythms fit a cosinor curve, an assumption that may not have been true when looking at adaptation to night shift. Hence an estimate of how good a fit was needed to be calculated, and the program created two criteria for this. Firstly, the program assessed whether the data were more likely to fit a straight line rather than a cosine curve, with a significant fit \((p<0.05)\) indicating that the probability of the data fitting a straight line was \(\leq 5\%\). Secondly, the percentage variability in the data accounted for by the cosinor curve was given, with a 100\% rhythm indicating a perfect fit. For all the studies, the criteria were used in such a way that an acrophase value was not accepted if the fit was not significant \((p>0.05)\) or the percentage rhythm was \(<80\%\).
The cosinor analysis program required data to be entered as rates of aMT6s production. The following calculation was used for each sampling period:

\[
\text{concentration (ng/ml) \times volume (ml) = rate of aMT6s production} \\
\text{duration of sampling period (hours) (ng/hour)}
\]

The data were entered into the cosinor analysis program to find the daily acrophase for each individual. A plot of acrophase time against day of study was then produced. For each group, the aMT6s rhythm was considered to have stabilised on the first day that the acrophase was no longer significantly different from the remaining days of study, as assessed by one-way ANOVA with Duncan’s New Multiple Range post-hoc testing.

For the baseline studies on the fixed oil installations, the rate of adaptation of the aMT6s rhythm was calculated from linear regression of the daily acrophases up to the day where the rhythm stabilised. The mean rate for each group was calculated from the averages of the individual rates. The group rates of adaptation were then compared by one-way ANOVA using group as a factor.

For the baseline studies on the floating drilling rig, day of study effects were assessed by one-way ANOVA with Duncan’s New Multiple Range post-hoc testing. Comparisons between groups were made by one-way ANOVA of raw data from all individuals within each group.

2.9.2 Glucose, insulin, TAG and NEFA data

The results for all four parameters were treated identically. Overall differences between the shifts were examined by first calculating the AUC over the time period of the sample collection for each subject. These data were then statistically tested by repeated measures ANOVA firstly from individuals who completed all three shifts, and then from all the individuals who completed the day and night shifts. This resulted in two different ANOVA results for the comparison between day shift and night shift.

Comparisons between identical time points in each shift were assessed by Student’s t test of treated data for each time point. The data was treated by expressing individual values as plus or minus the average basal values (time points -10 and 0 minutes) over the shifts for each individual.
2.10 Melatonin/placebo treatment

The treatment was assigned by a randomised, double-blind, crossover method. A different treatment was used for each leg, but neither the subjects nor the investigator had knowledge of which treatment was which.

2.10.1 Melatonin

As indicated earlier, this treatment was only used in the melatonin study where the subjects self-administered at home on leave. The subjects themselves reported that the biggest problem on leave was sleep disruption. Therefore the treatment was timed for bedtime, rather than for optimal phase shifting timing, to concentrate on trying to improve sleep quality and reduce problems resulting from sleep deficit. The treatment was conducted over four consecutive days in order to properly assess any changes in sleep and/or melatonin phase position.

The product used in the study was synthetic but identical to the natural compound in structure. It was provided in the form of a gelatin-lactose capsule (batch no. 0254M) by Penn Pharmaceuticals Ltd., Tredegar, Wales, who are licensed to sell this medication on a named patient basis. The capsules were stored below -25°C until ready for use. The dose used in this study was 5mg orally. The Department of Health do not require notification of trials using oral doses up to 10mg in healthy volunteers. The 5mg dose has been used successfully in more than 474 "jet lag" subjects during the last 10 years in Professor Arendt's work and in many other subjects in others' work, both for jet lag, delayed sleep phase insomnia, sleep disturbance in shift workers, in the blind and in the elderly (e.g. Arendt et al, 1987; Arendt and Aldhous, 1988; Jan et al, 1994; Wright et al, 1986; Zaidan et al, 1994; Garfinkel et al, 1995; Deacon & Arendt, 1996). The only reported side effects to date using melatonin to alleviate jet lag (in house study) are reported in Table 2-1.
Table 2-1: Side-effects of melatonin
Percentage side-effects reported more than once after taking melatonin (5mg) to alleviate jet lag (Arendt, University of Surrey).

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>Placebo (n=112)</th>
<th>Melatonin (n=474)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleepiness</td>
<td>1.78</td>
<td>8.3</td>
</tr>
<tr>
<td>Headache</td>
<td>2.7</td>
<td>1.65</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0.0</td>
<td>1.4</td>
</tr>
</tbody>
</table>

2.10.2 Placebo
The placebo was also provided by Penn Pharmaceuticals Ltd. in the form of a gelatin-lactose capsule (batch number 2738E), identical in colour, shape and size to the other treatment but contained no melatonin. It was used in exactly the same way to the melatonin treatment.
CHAPTER 3

BASELINE STUDY I - FIXED OIL PLATFORMS
3. Baseline study I - fixed oil platforms

3.1 Introduction

This study was conducted on two separate fixed oil platforms, approximately 15 miles apart, to assess whether the circadian rhythms of offshore oil workers were able to adapt to night shift. The urinary metabolite of melatonin, 6-sulphatoxymelatonin, was used as the main marker rhythm of circadian phase. On Platform 1 both drill crew and operations technician crew members were available allowing a primitive assessment of the phase-shifting ability of exercise (in this case a heavy versus light physical work load). Only operations technician crews were studied on both Platform 1 and Platform 2 in winter and summer, respectively, to allow an assessment of the effects of seasonal variation in light exposure on the rate of adaptation to night shift. The protocol for this study (see Appendix I) was approved by the University of Surrey's Advisory Committee on Ethics (USACE) in advance.

3.2 Specific methodology

Subjects were studied for the whole two weeks of their time offshore for both day shift and night shift. The following measurements were taken:
1) Three to four hourly urine collections during waking hours with one over-sleep collection.
2) Subjective alertness rating at the same time as urine collection.
3) Daily sleep log.
4) A shift work questionnaire.
5) Light exposure measurements.
6) Objective sleep (wrist actigraphy) was not obtained due to hardware problems.

3.3 Platform 1 - winter results

3.3.1 Sample population

The mean age and number of subjects studied for each group is given in Table 3-1. All subjects were male and in good health. Each subject acted as their own control, being studied on both day shift and night shift, except that two drill crew members and one technician were unavailable to be studied on day shift and one technician was unavailable to be studied on night shift.

* The winter study was conducted during November and December while the summer study was conducted between June and August.
Table 3-1: Mean age for the winter drill and technician groups.

<table>
<thead>
<tr>
<th></th>
<th>Age (mean ± sem)</th>
<th>Number in group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>years</td>
<td>Days</td>
</tr>
<tr>
<td>Drillers</td>
<td>44.9 ± 3.6</td>
<td>3</td>
</tr>
<tr>
<td>Operations technicians</td>
<td>36.7 ± 5.5</td>
<td>5</td>
</tr>
</tbody>
</table>

3.3.2 Light levels

The scotoperiod over the winter study period (provided by Bristow Helicopters, Safe Gothia) and shift pattern are shown in Figure 3-1. Light exposure during the study periods on night shift ranged between 50 and 400 lux (236 ± 42 lux, mean ± sem) and consisted of only artificial light (cool white fluorescent). Exposure during the day shift ranged between 50 and 1800 lux (673 ± 197 lux, mean ± sem) and consisted of both natural and artificial light. Lighting in the accommodation modules consisted mainly of artificial light, with only small windows on a few stairwells, and ranged between 150 and 500 lux (313 ± 42 lux, mean ± sem). Bedrooms were light tight with no windows.

The drill crew spent the majority of their work time outside on the pipe deck or on the drill floor. The drill floor had a large opening on one side facing out onto the pipe deck. Therefore, the crew were constantly exposed to the natural light-dark environment. The technician crew spent most of their work time traversing between and working in modules. Therefore their exposure to the natural light-dark environment was frequent but intermittent compared to the drill crew.

Figure 3-1: Winter shift pattern and scotoperiod.

The black bars represent the period of natural darkness with the horizontal square brackets showing the range of sunset and sunrise times.
3.3.3 6-sulphatoxymelatonin

The daily aMT6s acrophases for the drill crew and technician crew are plotted in Figure 3-2. Day 1 is the first day on the installation. The night shift acrophases phase delayed from a position of $0331h \pm 1.2$ hours (mean ± sem) and $0518h \pm 0.99$ hours to $1422h \pm 0.57$ hours and $1430h \pm 0.26$ hours in the drill crew and technician crew respectively. Figure 3-3 shows the daily acrophases for each group related to the night shift schedule. For each crew on night shift, the aMT6s acrophase position moved from the subjective day into the subjective night. No significant variation ($p>0.05$) in the aMT6s acrophase was evident during the day shift. Within each group there was no significant difference ($p>0.05$) between the first day shift acrophase and the first night shift acrophase. The acrophases were considered to have stabilised by days seven and five in the drill crew and technician crew respectively. The rates of phase shift (mean ± sem) up to the stabilisation days on night shift were $1.51 \pm 0.16$ h/day and $1.32 \pm 0.41$ h/day for the drill crew and technician crew respectively. There was no significant difference ($p>0.05$) in the rate of phase shift between the two groups.
Figure 3-2. aMT6s acrophase positions for the winter drill and technician crews.

(a) Drill crew (winter)

(b) Technician crew (winter)

Mean ± sem daily aMT6s acrophase positions during day shift (○) and night shift (■). Where error bars are not visible they are encompassed in the symbol, except for in (a) day shift 2, 3, 6, 8 and 14, and (b) day shift 12 and night shift 13, where n = 2. Asterisk (*) represents the days at which the rhythms were considered to have stabilised.
Mean ± sem daily aMT6s acrophase positions (●) superimposed on the shift schedule. Crossed bars represent time off the installation, black bars represent free time and white bars represent the work shift period.
3.3.4 Subjective sleep

The average sleep charts for the winter drill crew on day shift and night shift are shown in Figure 3-4. There were no significant (p>0.05) day of shift effects on sleep onset and offset during either day shift or night shift.

Figure 3-5 shows the group and individual sleep latencies. Individual latencies are only shown for subjects who completed both shifts. There were no significant (p>0.05) day of shift effects during day shift or night shift. There was no overall significant difference (p>0.05) between day shift and night shift for the group, but latency was significantly (p<0.05) greater on night shift day 9 compared to the same day on day shift. Sleep latency was significantly (p<0.05) higher during day shift compared to night shift in subject S4-JM.

Figure 3-6 shows the group and individual sleep durations. Individual durations are only shown for subjects who completed both shifts. There were no significant (p>0.05) day of shift effects during night shift. There was a significant (p<0.05) day of shift effect during day shift, with the duration on day 3 being significantly (p<0.05) longer than day 2, 4 and 6-13. There was no overall significant difference (p>0.05) between day shift and night shift for the group, but duration was significantly (p<0.01) shorter on day shift day 4 compared to the same day on night shift. There was no significant difference (p>0.05) between day shift and night shift in the individuals.

Figure 3-7 shows the group and individual sleep efficiencies. Individual efficiencies are only shown for subjects who completed both shifts. There were no significant (p>0.05) day of shift effects during day shift or night shift. There was no overall significant difference (p>0.05) between day shift and night shift for the group, nor between the same days of each shift. Sleep efficiency was significantly higher on day shift compared to night shift in subjects S1-GR (p<0.01) and S3-DT (p<0.001).

Figure 3-8 shows the group and individual sleep qualities. Individual qualities are only shown for subjects who completed both shifts. There were no significant (p>0.05) day of shift effects during day shift or night shift. However, during night shift there was a trend for lower sleep quality at the start of the shift compared to the remainder of the shift. There was no overall significant difference (p>0.05) between
Figure 3-4. Daily subjective sleep patterns for the winter drill crew.

(a) Night shift

(b) Day shift

Crossed bars represent no data, black bars represent sleep and white bars represent the time awake. Sleep onset and offset times are means and the error bars are standard error of the means.
Figure 3-5. Daily sleep latencies for the winter drill crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily sleep latencies relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem latencies during day shift (●) and night shift (■). The asterisk (*) indicates a significant difference (p<0.05) between shifts.
Figure 3-6. Daily sleep durations for the winter drill crew.

(a) Mean of all subjects

- DS ($n = 3$)
- NS ($n = 5$)

(b) Shift means for each subject

(a) Mean ± sem daily sleep durations relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem durations during day shift (■) and night shift (■).
Figure 3-7. Daily sleep efficiencies for the winter drill crew.

(a) Mean of all subjects

![Graph showing daily sleep efficiencies for DS (n=3) and NS (n=5).]

(b) Shift means for each subject

![Bar graph showing efficiency for subjects S1-GR, S3-DT, and S4-JM.]

(a) Mean ± sem daily sleep efficiency relative to individual means during day shift (○) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem efficiency during day shift (■) and night shift (■). Asterisks indicate significant differences between shifts (*p<0.01, **p<0.001).
Figure 3-8. Daily sleep qualities for the winter drill crew.

(a) Mean of all subjects

(b) Shift mean for each subject

(a) Mean ± sem daily sleep quality relative to individual means during day shift (○) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem quality during day shift (■) and night shift (■). Asterisks indicate significant differences between shifts (*p<0.05, **p<0.001).
day shift and night shift for the group, but quality was significantly (p<0.001) greater on night shift day 9 compared to the same day on day shift. Sleep quality was significantly better during day shift compared to night shift in subject S3-DT (p<0.001) and significantly worse in subject S4-JM (p<0.05).

The average sleep charts for the winter technician crew on day shift and night shift are shown in Figure 3-9. There were no significant (p>0.05) day of shift effects on sleep onset and offset during either day shift or night shift.

Figure 3-10 shows the group and individual sleep latencies. Individual latencies are only shown for subjects who completed both shifts. There were no significant (p>0.05) day of shift effects during day shift or night shift. There was no overall significant difference (p>0.05) between day shift and night shift for the group, nor between the same days of each shift. Sleep latency was significantly higher during day shift compared to night shift in subjects S1-TE (p<0.001) and S2-RD (p<0.05).

Figure 3-11 shows the group and individual sleep durations. Individual durations are only shown for subjects who completed both shifts. There were no significant (p>0.05) day of shift effects during day shift or night shift. There was no overall significant difference (p>0.05) between day shift and night shift for the group, nor between the same days of each shift. Sleep duration was significantly longer during night shift compared to day shift in subjects S1-TE (p<0.005) and S5-NR (p<0.005).

Figure 3-12 shows the group and individual sleep efficiencies. Individual efficiencies are only shown for subjects that completed both shifts. There were no significant (p>0.05) day of shift effects during day shift. There was a significant (p<0.001) day of shift effect during night shift, with the efficiency on days 2 and 3 being significantly (p<0.05) lower than the remaining days of the shift. There was no overall significant difference (p>0.05) between day shift and night shift for the group, but efficiency was significantly (p<0.05) greater on day 10 of night shift compared to the same day of day shift. Sleep efficiency was significantly higher during night shift.
Figure 3-9. Daily subjective sleep patterns for the winter technician crew.

(a) Night shift

(b) Day shift

Crossed bars represent no data, black bars represent sleep and white bars represent the time awake. Sleep onset and offset times are means and the error bars are standard error of the means.
Figure 3-10. Daily sleep latencies for the winter technician crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily sleep latencies relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem latencies during day shift (●) and night shift (■). Asterisks indicate a significant difference between shifts (*p<0.05, **p<0.001).
Figure 3-11. Daily sleep durations for the winter technician crew.

(a) Mean of all subjects

(b) Shift mean for each subject

(a) Mean ± sem daily sleep durations relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. 
(b) Individual mean ± sem durations during day shift (■) and night shift (■). Asterisks indicate significant differences between shifts (*p<0.005).
Figure 3-12. Daily sleep efficiencies for the winter technician crew.

(a) Mean of all subjects

- DS (n = 5)
- NS (n = 5)

![Graph showing daily sleep efficiencies for DS and NS.]

(b) Shift means for each subject

- S1-TE
- S2-RD
- S3-AW
- S5-NR

![Bar chart showing individual means for each subject.]

(a) Mean ± sem daily sleep efficiency relative to individual means during day shift (○) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem efficiency during day shift (■) and night shift (■). Asterisks indicate significant differences between shifts (*p<0.05, **p=0.001).
compared to day shift in subject S1-TE (p<0.001) and lower in subject S2-RD (p<0.05).

Figure 3-13 shows the group and individual sleep qualities. Individual qualities are only shown for subjects that completed both shifts. There were no significant (p>0.05) day of shift effects during day shift or night shift. There was no overall significant difference (p>0.05) between day shift and night shift for the group, nor between the same days of each shift. Sleep quality was significantly better during night shift compared to day shift in subject S1-TE (p<0.05).

3.3.5 Sleep parameters in relation to phase

Figure 3-14 shows the relationship between aMT6s acrophase and the sleep parameters of subjective quality, duration, efficiency and latency for the winter drill crew on night shift. There was a significant correlation between aMT6s acrophase position and two of the sleep parameters, with a delay in acrophase position corresponding to a significant increase in sleep quality (r=0.53, df=45, p<0.001) and efficiency (r=0.34, df=45, p<0.05). There was no significant correlation between aMT6s acrophase position and sleep duration (r=0.03, df=45, p>0.05) and latency (r=0.09, df=45, p>0.05).

Figure 3-15 shows the relationship between aMT6s acrophase and the sleep parameters of subjective quality, duration, efficiency and latency for the winter technician crew on night shift. There was a significant correlation between aMT6s acrophase position and two of the sleep parameters, with a delay in acrophase position corresponding to a significant increase in sleep efficiency (r=0.47, df=45, p<0.001) and latency (r=0.35, df=45, p<0.05). There was no significant correlation between aMT6s acrophase position and sleep quality (r=0.13, df=45, p>0.05) and duration (r=0.17, df=45, p>0.05).

In order to further examine the relation between sleep efficiency and phase, the total duration of daily mid-sleep awakenings was also compared to phase. Figure 3-16 shows this relationship for both groups. There was a significant correlation for both the winter drill crew (r=0.41, df=45, p<0.01) and the winter technician crew (r=0.57, df=45, p<0.001), with a delay in aMT6s acrophase corresponding to a decrease in the total duration of awakenings.
Figure 3-13. Daily sleep qualities for the winter technician crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily sleep quality relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem quality during day shift (●) and night shift (■). Asterisks indicate significant differences between shifts (*p<0.05).
Figure 3-14. Correlation between aMT6s acrophase and sleep parameters for the winter drill crew. (Night shift values relative to the day shift mean).

(a) Sleep quality
\[ r = 0.53, \text{df}=45, p<0.001 \]

(b) Sleep duration
\[ r = 0.03, \text{df}=45, p>0.05 \]

(c) Sleep efficiency
\[ r=0.34, \text{df}=45, p<0.05 \]

(d) Sleep latency
\[ r=0.09, \text{df}=45, p>0.05 \]
Figure 3-15. Correlation between aMT6s acrophase and sleep parameters for the winter technician crew. (Night shift values relative to the day shift mean).

(a) Sleep quality
\[ r = 0.13, \text{df}=45, p>0.05 \]

(b) Sleep duration
\[ r = 0.17, \text{df}=45, p>0.05 \]

(c) Sleep efficiency
\[ r=0.47 \text{ df}=45, p<0.001 \]

(d) Sleep latency
\[ r=0.35 \text{ df}=45, p<0.05 \]
Figure 3-16. Correlation between aMT6s acrophase and duration of awakenings for the winter drill and technician crew. (Night shift values relative to the day shift mean).

(a) Winter drill crew

\[ r = 0.41 \text{ df } 45, p<0.01 \]

Awakenings relative to shift average

\[ \text{aMT6s acrophase relative to day shift mean} \]

(b) Winter technician crew

\[ r = 0.57 \text{ df } 45, p<0.001 \]

Awakenings relative to shift mean

\[ \text{aMT6s acrophase relative to day shift mean} \]
3.3.6 Subjective alertness

The majority of subjects did not have sufficient data points to assess alertness acrophase positions by cosinor analysis. Therefore, area under the curve analysis was used instead as described in the methods (section 2.8.3). For consistency this method of analysis was used throughout the remaining baseline studies.

Two examples of alertness patterns over the work period for the winter drill crew are shown in Figures 3-17 and 3-18. Figure 3-19 shows the group and individual alertness total AUCs for the winter drill crew over the work period. Individual alertness AUCs are only shown for subjects that completed both shifts. There were no significant (p>0.05) day of shift effects during day shift. There was a significant (p<0.001) day of shift effect during night shift, with the alertness on day 1 being significantly (p<0.05) lower than the remaining days of the shift, day 2 being significantly (p<0.05) lower than days 6, 10 to 12 and 14, and day 3 and 4 being significantly (p<0.05) lower than days 6, 7 and 9 to 14. Night shift was significantly (p<0.05) lower than day shift overall, with alertness being significantly (p<0.05) greater on day 1 of day shift and day 10 of night shift compared to the same day of the opposite shift. Alertness was significantly higher during day shift compared to night shift in subjects S1-GR (p<0.05), S3-DT (p<0.001) and S4-JM (p<0.001).

Two examples of alertness patterns over the work period for the winter technician crew are shown in Figures 3-20 and 3-21. Figure 3-22 shows the group and individual alertness total AUCs for the winter technician crew over the work period. Individual alertness AUCs are only shown for subjects that completed both shifts. There were no significant (p>0.05) day of shift effects during day shift. There was a significant (p<0.005) day of shift effect during night shift, with the alertness on day 1 and 4 being significantly (p<0.05) lower than days 3 and 12, day 2 being significantly (p<0.05) lower than days 3, 5, 6 and 8 to 12, and day 7 being significantly (p<0.05) lower than day 3. There was no overall significant difference (p>0.05) between day shift and night shift for the group, but alertness was significantly (p<0.05) greater on day 1 of day shift and day 10 of night shift compared to the same day of the opposite shift. Alertness was significantly lower during day shift compared to night shift in subjects S2-RD (p<0.005) and S3-AW (p<0.01).
Figure 3-17. Subjective alertness for subject S1-GR.

Subjective alertness on day shift (●) and night shift (■) for subject S1-GR. Time is relative to the centre of the work shift. Only the period from two hours before the work shift through to two hours after the work shift is shown.
Subjective alertness on day shift (●) and night shift (■) for subject S3-DT. Time is relative to the centre of the work shift. Only the period from two hours before the work shift through to two hours after the work shift is shown.
Figure 3-19. Group and individual alertness total AUCs for the winter drill crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily alertness AUCs relative to individual means during day shift (○) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem alertness AUCs during day shift (■) and night shift (■). The asterisks indicate a significant difference between shifts (*p<0.05, **p<0.001).
Subjective alertness on day shift (○) and night shift (■) for subject S2-RD. Time is relative to the centre of the work shift. Only the period from two hours before the work shift through to two hours after the work shift is shown.
Figure 3-21. Subjective alertness for subject S5-NR.

Subjective alertness on day shift (●) and night shift (■) for subject S5-NR. Time is relative to the centre of the work shift. Only the period from two hours before the work shift through to two hours after the work shift is shown.
Figure 3-22. Group and individual alertness total AUCs for the winter technician crew

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily alertness AUCs relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem alertness AUCs during day shift (●) and night shift (■). The asterisks indicate a significant difference between shifts (*p<0.01, **p<0.005).
3.3.7 Alertness in relation to phase

Figure 3-23 shows the relationship between aMT6s acrophase and the total, first half of shift and second half of shift AUCs for the winter drill crew. There was a significant correlation between aMT6s acrophase position and two of the alertness parameters, with a delay in acrophase position corresponding to a significant increase in total AUC alertness (r=0.38, df=50, p<0.01) and second half of shift AUC (r=0.70, df=50, p<0.001). There was no significant correlation between aMT6s acrophase position and first half of shift AUC (r=0.25, df=50, p>0.05).

Figure 3-24 shows the relationship between aMT6s acrophase and the total, first half of shift and second half of shift AUCs for the winter technician crew. There was a significant correlation between aMT6s acrophase position and two of the alertness parameters, with a delay in acrophase position corresponding to a significant increase in total AUC alertness (r=0.33, df=42, p<0.05) and second half of shift AUC (r=0.58, df=42, p<0.001). There was no significant correlation between aMT6s acrophase position and first half of shift AUC (r=0.20, df=42, p>0.05).

3.4 Platform 2 - summer results

3.4.1 Sample population

The mean age and number of subjects studied for the group is given in Table 3-2. All subjects were male and in good health. Nine subjects were studied on both day shift and night shift, nine subjects were studied on night shift only and five subjects were studied on day shift only.

Table 3-2: Mean age for the summer technician groups.

<table>
<thead>
<tr>
<th>Age (mean ± sem) years</th>
<th>Number in group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Days</td>
</tr>
<tr>
<td>Operations technicians</td>
<td>37.4 ± 2.0</td>
</tr>
</tbody>
</table>

3.4.2 Light levels

The scotoperiod over the summer study period (provided by Bristow Helicopters, Safe Gothia) and shift pattern are shown in Figure 3-25. Light exposure
Figure 3-23. Correlation between aMT6s acrophase and alertness for the winter drill crew.

(a) Total AUCs vs acrophase

$\text{r} = 0.38$, df = 50, $p<0.01$

(b) 1st half AUCs vs acrophase

$\text{r} = 0.25$, df = 50, $p>0.05$

(c) 2nd half AUCs vs acrophase

$\text{r} = 0.70$, df = 50, $p<0.001$
Figure 3-24. Correlation between aMT6s acrophase and alertness for the winter technician crew.

(a) Total AUCs vs acrophase

\[ r = 0.33, \text{ df = 42, } p < 0.05 \]

(b) Alertness AUC relative to shift mean

\[ r = 0.20, \text{ df = 42, } p > 0.05 \]

(c) Alertness AUC relative to shift mean

\[ r = 0.58, \text{ df = 42, } p < 0.001 \]
during the study periods on night shift ranged between 50 and 2000 lux (716 ± 253 lux, mean ± sem) and consisted of natural and artificial light (cool white fluorescent). Exposure during the day shift ranged between 50 and 2300 lux (1513 ± 308 lux, mean ± sem) and consisted of both natural and artificial light. Lighting in the accommodation modules was identical to that in the winter (section 3.3.2).

As mentioned earlier, the technician crew spent most of their work time traversing between and working in modules. Therefore their exposure to the natural light-dark environment was frequent but intermittent.

**Figure 3-25. Summer shift pattern and scotoperiod.**

![Summer shift pattern and scotoperiod](image)

The black bar represents the period of natural darkness with the horizontal square brackets showing the range of sunset and sunrise times.

3.4.3 6-sulphatoxymelatonin

The daily aMT6s acrophases for the group are plotted in Figure 3-26. Day 1 is the first day on the installation. The night shift acrophases phase delay from a position of 0600h ± 1.03 hours (mean ± sem) to 1443h ± 0.25 hours. Figure 3-27 shows the daily acrophases for the group related to the night shift schedule. On night shift the aMT6s acrophase position moved from the subjective day into the subjective night. No significant variation (p>0.05) in the aMT6s acrophase was evident during the day shift. There was no significant difference (p>0.05) between the first day shift acrophase and the first night shift acrophase. The acrophases were considered to have stabilised by day five. The rate of phase shift (mean ± sem) up to day five on night shift was 1.77 ± 0.31 h/day for the group. One subject (S11-CS) was excluded from the results because his rhythm appeared to have phase advanced (1.27 h/day) to the adapted phase position as seen in Figure 3-28.
Figure 3-26. aMT6s acrophase positions for the summer technician crew.

Mean ± sem daily aMT6s acrophase positions during day shift (●) and night shift (■). Where error bars are not visible they are encompassed in the symbol, except for on day shift 15 and night shift 14, where n = 2. Asterisk (*) represents the days at which the rhythms were considered to have stabilised.
Figure 3-27. Night shift aMT6s acrophases in relation to the shift schedule for the summer technician crews.

Night shift mean ± sem daily aMT6s acrophase positions (*) superimposed on the shift schedule. Crossed bars represent time off the installation, black bars represent free time and white bars represent the work shift period.
Figure 3-28. Night shift aMT6s acrophases in relation to the shift schedule for subject S11-CS.

Night shift daily aMT6s acrophase positions (•) superimposed on the shift schedule. Crossed bars represent time off the installation, black bars represent free time and white bars represent the work shift period.
3.4.4 Subjective sleep

The average sleep charts for the summer technician crew on day shift and night shift are shown in Figure 3-29. There were no significant (p>0.05) day of shift effects on sleep onset and offset during day shift. During night shift, a significant (p<0.05) day of shift effect was observed in sleep onset, with day 2 being significantly (p<0.05) earlier than the remaining days of the shift. Sleep offset also showed a significant (p<0.001) day of shift effect, with significantly (p<0.05) earlier offsets on day 2 compared to days 4 and 6 to 14, day 3 compared to days 6 to 14, and day 5 compared to day 14.

Figure 3-30 shows the group and individual sleep latencies. Individual latencies are only shown for subjects who completed both shifts. There were no significant (p>0.05) day of shift effects during day shift or night shift. There was no overall significant difference (p>0.05) between day shift and night shift for the group, nor between the same days of each shift. Sleep latency was significantly higher during day shift compared to night shift in subjects S10-KB (p<0.05), S14-TG (p<0.001), S15-JJ (p<0.01), S18-DC (p<0.005) and S21-DG (p<0.001). Only one subject out of the nine had a lower, but non-significant (p>0.05), sleep latency on day shift compared to night shift.

Figure 3-31 shows the group and individual sleep durations. Individual durations are only shown for subjects who completed both shifts. There were no significant (p>0.05) day of shift effects during day shift or night shift. There was no overall significant difference (p>0.05) between day shift and night shift for the group, but duration was significantly (p<0.05) longer on days 6 and 12 of day shift compared to the same days on night shift. Sleep duration was significantly longer during night shift compared to day shift for subjects S3-PS (p<0.05), S4-CD (p<0.01), S10-KB (p=0.001) and S21-DG (p<0.01). Duration was significantly shorter during night shift compared to day shift for subject S15-JJ (p<0.005).

Figure 3-32 shows the group and individual sleep efficiencies. Individual efficiencies are only shown for subjects who completed both shifts. There were no significant (p>0.05) day of shift effects during day shift or night shift. There was no overall significant difference between (p>0.05) day shift and night shift for the group,
Figure 3-29. Daily subjective sleep patterns for the summer technician crew.

(a) Night shift

Crossed bars represent no data, black bars represent sleep and white bars represent the time awake. Sleep onset and offset times are means and the error bars are standard error of the means.

(b) Day shift
Figure 3-30. Daily sleep latencies for the summer technician crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily sleep latencies relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem latencies during day shift (●) and night shift (■). Asterisks indicate a significant difference between shifts (*p<0.05, **p<0.01, ***p<0.005, †p<0.001).
Figure 3-31. Daily sleep durations for the summer technician crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily sleep durations relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem duration during day shift (■) and night shift (■). Asterisks indicate a significant difference between shifts (*p<0.05, **p<0.01, ***p<0.005, †p=0.001).
Figure 3-32. Daily sleep efficiencies for the summer technician crew.

(a) Mean of all subjects

- DS ($n = 14$)
- NS ($n = 18$)

(b) Shift means for each subject

(a) Mean ± sem daily sleep efficiency relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem efficiency during day shift (■) and night shift (■). Asterisks indicate significant differences between shifts (*p < 0.05, **p = 0.005).
but efficiency was significantly (p<0.05) greater on day shift day 3 compared to the same day on night shift. Sleep efficiency was higher on night shift compared to day shift for subjects S10-KB (p<0.05) and S21-DG (p<0.05), and lower on night shift for subject S15-JJ (p=0.005).

Figure 3-33 shows the group and individual sleep qualities. Individual qualities are only shown for subjects who completed both shifts. There were significant day of shift effects during day shift (p<0.05) and night shift (p<0.001). On day shift, sleep quality was lower on day 1 compared to days 6, 7, 10, 11 and 14, and days 3 and 4 compared to days 6 and 10. On night shift, sleep quality was lower on day 2 compared to days 6 to 14, day 3 compared to days 5 to 14, and day 4 compared to days 7 to 14. There was no overall significant difference (p>0.05) between day shift and night shift for the group, but quality was significantly (p<0.05) higher on day shift day 3 and night shift day 12 compared to the same day of the opposite shift. Sleep quality was better on day shift compared to night shift for subjects S15-JJ (p<0.005) and S20-MB (p<0.05), and worse on day shift for subject S21-DG (p=0.001).

3.4.5 Sleep parameters in relation to phase

Figure 3-34 shows the relationship between aMT6s acrophase and the sleep parameters of subjective quality, duration, efficiency and latency for the summer technician crew during night shift. There was a significant correlation between aMT6s acrophase position and two of the sleep parameters, with a delay in acrophase position corresponding to a significant increase in sleep quality (r=0.29, df=153, p<0.01) and duration (r=0.23, df=154, p<0.05). There was no significant correlation between aMT6s acrophase position and sleep efficiency (r=0.05, df=159, p>0.05) and latency (r=0.03, df=156, p>0.05).

3.4.6 Subjective alertness

Two examples of alertness patterns over the work period for the summer technician crew are shown in Figures 3-35 and 3-36. Figure 3-37 shows the group and individual alertness total AUCs for the summer technician crew over the work period. Individual alertness AUCs are only shown for subjects that completed both shifts. There were no significant (p>0.05) day of shift effects during day shift. There
Figure 3-33. Daily sleep qualities for the summer technician crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily sleep quality relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem quality during day shift (■) and night shift (■). Asterisks indicate significant differences between shifts (*p<0.05, **p<0.005, *†p=0.001).
Figure 3-34. Correlation between aMT6s acrophase and sleep parameters for the summer technician crew.

(a) Sleep quality

\[ r = 0.29, \text{df}=153, p<0.01 \]

(b) Sleep duration

\[ r = 0.23, \text{df}=154, p<0.05 \]

(c) Sleep efficiency

\[ r = 0.05, \text{df}=159, p>0.05 \]

(d) Sleep latency

\[ r = 0.03, \text{df}=156, p>0.05 \]
Subjective alertness on day shift (○) and night shift (■) for subject S3-PS. Time is relative to the centre of the work shift. Only the period from two hours before the work shift through to two hours after the work shift is shown.
Subjective alertness on day shift (●) and night shift (■) for subject S14-TG. Time is relative to the centre of the work shift. Only the period from two hours before the work shift through to two hours after the work shift is shown.
Figure 3-37. Group and individual alertness total AUCs for the summer technician crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily alertness AUCs relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem alertness AUCs during day shift (■) and night shift (■). The asterisks indicate a significant difference between shifts (*p<0.05, **p<0.01, ***p<0.005, †p<0.001).
was a significant \((p<0.001)\) day of shift effect during night shift, with the alertness on day 1 being significantly \((p<0.05)\) lower than the remaining days of shift, day 2 being significantly \((p<0.05)\) lower than days 5 and 8 to 14, and days 3 and 7 being significantly \((p<0.05)\) lower than day 13. There was no overall significant difference \((p>0.05)\) between day shift and night shift for the group, but alertness was significantly \((p<0.05)\) greater on day 2 of day shift and day 3 of night shift compared to the same day of the opposite shift when looking solely at individuals who did both shifts. Alertness was significantly higher during day shift compared to night shift in subjects S18-DC \((p<0.005)\), S19-IC \((p<0.01)\) and S21-DG \((p<0.001)\). Alertness was significantly higher during night shift compared to day shift in subject S10-KB \((p<0.05)\).

### 3.4.7 Alertness in relation to phase

Figure 3-38 shows the relationship between aMT6s acrophase and the total, first half of shift and second half of shift AUCs for the summer technician crew. There was a significant correlation between aMT6s acrophase position and two of the alertness parameters, with a delay in acrophase position corresponding to a significant increase in total AUC alertness \((r=0.30, \text{df}=125, p<0.01)\) and second half of shift AUC \((r=0.34, \text{df}=125, p<0.001)\). There was no significant correlation between aMT6s acrophase position and first half of shift AUC \((r=0.18, \text{df}=125, p>0.05)\).

### 3.5 Comparison between winter and summer

#### 3.5.1 6-sulphatoxymelatonin

The aMT6s acrophases for the three groups are shown in Figure 3-39. The rates of phase shift for each group on night shift are shown in Table 3-3. In the case of the summer technician crew, the data for the subject who phase advanced was not included in the calculation. There was no significant difference \((p>0.05)\) in the rate of adaptation between the groups.
Table 3-3: Rates of adaptation for the three groups assessed by linear regression up to the group stabilisation days.

<table>
<thead>
<tr>
<th>Group</th>
<th>Total number</th>
<th>Number studied on night shift</th>
<th>Rate of adaptation (mean ± sem)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drill crew (winter)</td>
<td>5</td>
<td>5</td>
<td>1.51 ± 0.16 h/day</td>
</tr>
<tr>
<td>Technician crew (winter)</td>
<td>6</td>
<td>5</td>
<td>1.32 ± 0.41 h/day</td>
</tr>
<tr>
<td>Technician crew (summer)</td>
<td>23</td>
<td>18 *</td>
<td>1.77 ± 0.31 h/day</td>
</tr>
</tbody>
</table>

* Note that one subject showed a phase advance of his aMT6s acrophase and was therefore excluded from the analysis, resulting in n = 17.
Figure 3-38. Correlation between aMT6s acrophase and alertness for the summer technician crew.

(a) Total AUCs vs acrophase

\[ r = 0.30 \text{ df}=125 \text{ p}<0.01 \]

(b) 1st half AUCs vs acrophase

\[ r = 0.18 \text{ df}=125 \text{ p}>0.05 \]

(c) 2nd half AUCs vs acrophase

\[ r = 0.34 \text{ df}=125 \text{ p}<0.001 \]
Figure 3-39. aMT6s acrophase positions for the winter drill crew, winter technician crew and summer technician crew.

Mean ± sem daily aMT6s acrophase positions for the winter drill crew (■ n = 3 day shift, n= 5 night shift), winter technician crew (● n = 5 day shift, n = 5 night shift) and summer technician crew (♦ n = 14 day shift, n = 17 night shift).
CHAPTER 4

BASELINE STUDY II - FLOATING DRILLING RIG
4. Baseline study II - floating drilling rig

4.1 Introduction

The purpose of this study was to examine the adaptation of circadian rhythms to night shift under a different shift schedule and to determine if seasonality played a role in this process. The only available installation was a floating drilling rig with no operation technicians but a large drill crew. The rig was situated approximately 10 miles from the other two platforms. As before, 6-sulphatoxymelatonin was used as the main rhythm marker of circadian phase. Two crews were studied; one crew in winter and the other in spring. The University of Surrey’s Advisory Committee on Ethics (USACE) were happy for the protocol from Baseline Study I to cover this work.

4.2 Specific methodology

Subjects were studied for the whole two weeks of their time offshore. During this time they completed a full day shift week and night shift week. The following measurements were taken:

1) Three to four hourly urine collections during waking hours with one over-sleep collection.
2) Subjective alertness rating at the same time as urine collection.
3) Daily sleep log.
4) Constant wrist actigraphy.
5) A shift work questionnaire.
6) Light exposure measurements.

4.3 Winter results

4.3.1 Sample population

The mean age and number of subjects studied for the group is given in Table 4-1. All subjects were male and in good health.

* The winter study was conducted in December while the spring study was conducted in March.
Table 4-1: Mean age for the winter drill crew.

<table>
<thead>
<tr>
<th>Drill crew (winter)</th>
<th>Mean ± sem age (years)</th>
<th>Number in group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>34.6 ± 2.1</td>
<td>11</td>
</tr>
</tbody>
</table>

4.3.2 Light levels

The scotoperiod over the winter study period (provided by Bristow Helicopters, Safe Gothia) and shift pattern are shown in Figure 4-1. Light exposure during the study periods on night shift ranged between 70 and 1400 lux (691 ± 196 lux, mean ± sem) and consisted of natural and artificial light (cool white fluorescent). Exposure during the day shift ranged between 70 and 1600 lux (633 ± 217 lux, mean ± sem) and consisted of both natural and artificial light. Lighting in the accommodation modules consisted mainly of artificial light, with only small windows in the cinema room, and ranged between 100 and 450 lux (260 ± 51 lux, mean ± sem). Bedrooms were light tight with no windows.

The drill crew spent the majority of their work time outside on the pipe deck or on the drill floor. The drill floor had a large opening on one side facing out onto the pipe deck. Therefore, the crew were constantly exposed to the natural light-dark environment.

Figure 4-1. Winter shift pattern and scotoperiod.

The black bars represent the period of natural darkness with the horizontal square brackets showing the range of sunset and sunrise times.

4.3.3 6-sulphatoxymelatonin

The daily aMT6s acrophases for the winter crew are shown in Figure 4-2. Day one is the first day on shift and day eight is the period of rapid changeover. The day shift acrophases phase delayed slightly, from a position of 0541h ± 0.38 hours
Figure 4-2. aMT6s acrophase positions for the winter drill crew.

Mean ± sem daily aMT6s acrophase positions (■). Where error bars are not visible they are encompassed in the symbol.
(mean ± sem) to 0651h ± 0.29 hours, in line with the delay of the sleep and work periods. However, following the rapid change over (day 8), the crew showed only a slight, but non-significant (p>0.05), phase advance to 0506h ± 1.45 hours (mean ± sem) by day 14. The relation between the acrophase positions and the shift pattern is shown in Figure 4-3. The aMT6s acrophases remained in the middle of the work period throughout night shift.

4.3.4 Subjective sleep

For all sleep analysis, the sleep during the rapid change over between shifts (day 8) was not used in any calculation. The average sleep chart for the winter drill crew is shown in Figure 4-4. There were no significant (p>0.05) day of shift effects on sleep onset and offset during either day shift or night shift.

Figure 4-5 shows the group and individual sleep latencies. There were no significant (p>0.05) day of shift effects during the whole fortnight, day shift or night shift. There was no overall significant difference (p>0.05) between day shift and night shift for the group. Sleep latency was significantly longer during day shift compared to night shift in subjects S3-DP (p<0.005) and S14-RD (p<0.05).

Figure 4-6 shows the group and individual sleep durations. There were no significant (p>0.05) day of shift effects during the day shift or night shift. However, there was a significant (p<0.005) day of shift effect when examining the whole fortnight, with the duration on days 3 and 6 being significantly (p<0.05) longer than day 10, days 4 and 5 being significantly (p<0.05) longer than days 9 to 11 and 14, and day 7 being significantly (p<0.05) longer than days 10 and 11. There was an overall significantly (p<0.05) higher sleep duration during day shift compared to night shift for the group. Sleep duration was significantly longer during day shift compared to night shift in subjects S5-CR (p<0.005), S7-RM (p<0.05) and S13-DC (p<0.05).

Figure 4-7 shows the group and individual sleep efficiencies. There were no significant (p>0.05) day of shift effects during the whole fortnight, day shift or night shift. However, during night shift there was a trend for lower sleep efficiency at the start of the shift compared to the remainder of the shift. There was no overall significant difference (p>0.05) between day shift and night shift for the group. Sleep
Figure 4-3. aMT6s acrophases in relation to the shift schedule for the winter drill crew.

Mean ± sem daily aMT6s acrophase positions (*) on the shift schedule. Crossed bars represent time off the installation, black bars represent free time and white bars represent the work shift period.
Figure 4-4. Daily subjective sleep patterns for the winter drill crew.

Crossed bars represent no data, black bars represent sleep and white bars represent the time awake. Sleep onset and offset times are means and the error bars are standard error of the means.
Figure 4-5. Daily subjective sleep latencies for the winter drill crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily subjective sleep latencies relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem subjective latencies during day shift (■) and night shift (■). The asterisks indicate a significant difference between shifts (*p<0.05, **p<0.005).
Figure 4-6. Daily subjective sleep durations for the winter drill crew.

(a) Mean of all subjects

Duration relative to shift mean (hours)

-3 -2 -1 0 1 2 3

Study day

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

(b) Shift means for each subject

Duration (hours)

1 2 3 4 5 6 7 8 9 10

Subjects

S1-MS S2-RW S3-DP S4-IR S5-CR S7-RM S8-BM S13-DC S14-RD S15-JE

(a) Mean ± sem daily subjective sleep durations relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem subjective durations during day shift (●) and night shift (■). The asterisks indicate a significant difference between shifts (*p<0.05, **p<0.005).
Figure 4-7. Daily subjective sleep efficiencies for the winter drill crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily subjective sleep efficiency relative to individual means during
day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each
individual on each shift. (b) Individual mean ± sem subjective efficiency during day
shift (■) and night shift (■). Asterisks indicate significant differences between shifts
(*p<0.05).
efficiency was significantly higher on night shift compared to day shift in subjects S2-RW (p<0.05) and S14-RD (p<0.05).

Figure 4-8 shows the group and individual sleep qualities. There were no significant (p>0.05) day of shift effects during the whole fortnight, day shift or night shift. There was no overall significant difference (p>0.05) between day shift and night shift for the group. Sleep quality was significantly (p<0.05) better during day shift compared to night shift in subjects S2-RW, S6-SF and S13-DC.

In order to examine the differences in sleep duration more closely the total duration of mid-sleep awakenings was also assessed. Figure 4-9 shows the group and individual duration of awakenings for the winter crew. There were no significant (p>0.05) day of shift effects during the whole fortnight, day shift or night shift. There was no overall significant difference (p>0.05) between day shift and night shift for the group. Total duration of awakenings was significantly longer during day shift compared to night shift in subjects S2-RW (p<0.005) and S8-BM (p<0.05).

4.3.5 Objective sleep - actigraphy

There were no significant (p>0.05) day of shift effects on sleep onset and offset during either day shift or night shift. Figure 4-10 shows the group and individual sleep latencies. There were no significant (p>0.05) day of shift effects during the whole fortnight or night shift. However, there was a significant (p<0.005) day of shift effect when examining the day shift alone, with the latency on day 5 being significantly (p<0.05) longer than days 3, 4 and 6. There was no overall significant difference (p>0.05) between day shift and night shift for the group. Sleep latency was significantly longer during day shift compared to night shift in subject S7-RM (p<0.05).

Figure 4-11 shows the group and individual sleep durations. There were no significant (p>0.05) day of shift effects during the whole fortnight, day shift or night shift. There was no overall significant difference (p>0.05) between day shift and night shift for the group. There were no significant differences (p>0.05) between day shift and night shift amongst individuals.

Figure 4-12 shows the group and individual sleep efficiencies. There were no significant (p>0.05) day of shift effects during the whole fortnight, day shift or night shift.
Figure 4-8. Daily subjective sleep qualities for the winter drill crew.

(a) Mean of all subjects

(b) Shift mean for each subject

(a) Mean ± sem daily subjective sleep quality relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem subjective quality during day shift (■) and night shift (■). Asterisks indicate a significant difference between shifts (*p<0.05).
Figure 4-9. Daily subjective duration of awakenings for the winter drill crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily subjective total duration of awakenings relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem subjective duration of awakenings during day shift (■) and night shift (■). Asterisks indicate a significant difference between shifts (*p<0.05, **p<0.005).
Figure 4-10. Daily objective sleep latencies for the winter drill crew.

(a) Mean of all subjects

Latency relative to shift mean (mins)

Study day

(b) Shift means for each subject

Latency (mins)

Subjects

(a) Mean ± sem daily objective sleep latencies relative to individual means during day shift (○) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem objective latencies during day shift (■) and night shift (■). Asterisk indicates a significant difference between shifts (*p<0.05).
Figure 4-11. Daily objective sleep durations for the winter drill crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily objective sleep durations relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem objective durations during day shift (■) and night shift (■).
Figure 4-12. Daily objective sleep efficiencies for the winter drill crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily objective sleep efficiency relative to individual means during day shift (•) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem objective efficiency during day shift (■) and night shift (■). Asterisk indicates a significant difference between shifts (*p<0.005).
shift. However, during night shift there was a trend for higher sleep efficiency at the start of the shift compared to the remainder of the shift. There was no overall significant difference (p>0.05) between day shift and night shift for the group. Sleep efficiency was significantly higher on night shift compared to day shift in subject S2-RW (p<0.005).

4.3.6 Sleep parameters in relation to phase

Figure 4-13 shows the relationship between aMT6s acrophase and the subjective sleep parameters for the winter drill crew during night shift. There was no significant correlation between aMT6s acrophase position and sleep latency (r=-0.21, df=39, p>0.05), duration (r=-0.18, df=39, p>0.05), efficiency (r=0.04, df=39, p>0.05) or quality (r=0.05, df=39, p>0.05).

Figure 4-14 shows the relationship between aMT6s acrophase and the objective sleep parameters for the winter drill crew during night shift. There was no significant correlation between aMT6s acrophase position and sleep latency (r=0.26, df=17, p>0.05), duration (r=-0.07, df=19, p>0.05) or efficiency (r=-0.13, df=17, p>0.05).

4.3.7 Alertness

Two examples of alertness patterns over the work period for the summer technician crew are shown in Figures 4-15 and 4-16. Figure 4-17 shows the group and individual alertness total AUCs for the winter drill crew over the work period. There were no significant (p>0.05) day of shift effects when examining day shift alone. However there was a significant day of shift effect during the whole fortnight (p<0.005) and during night shift (p<0.005), with the alertness on days 4 and 9 being significantly (p<0.05) lower than days 3 and 11 to 13, and days 10 and 14 being significantly (p<0.05) lower than day 13. Alertness was overall significantly higher (p<0.001) on day shift compared to night shift for the group. Alertness was significantly higher during day shift compared to night shift in subjects S1-MS (p<0.01), S2-RW (p<0.005), S3-DP (p<0.001), S4-IR (p<0.001), S13-DC (p<0.005) and S14-RD (p<0.05).
Figure 4-13. Correlation between aMT6s acrophase and subjective sleep parameters for the winter drill crew.

(a) Sleep latency

(b) Sleep duration

(c) Sleep efficiency

(d) Sleep quality

$r = -0.21, df = 39, p > 0.05$

$r = -0.18, df = 39, p > 0.05$

$r = 0.04, df = 39, p > 0.05$

$r = 0.05, df = 39, p > 0.05$
Figure 4-14. Correlation between aMT6s acrophase and objective sleep parameters for the winter drill crew.

(a) Sleep latency
\[ r = 0.26, \text{df}=17, p > 0.05 \]

(b) Sleep duration
\[ r = -0.07, \text{df}=19, p > 0.05 \]

(c) Sleep efficiency
\[ r = -0.13, \text{df}=17, p > 0.05 \]
Subjective alertness on day shift (○) and night shift (■) for subject S2-RW. Time is relative to the centre of the work shift. Only the period from two hours before the work shift through to two hours after the work shift is shown.
Figure 4-16. Subjective alertness for subject S6-SF.

Subjective alertness on day shift (●) and night shift (■) for subject S6-SF. Time is relative to the centre of the work shift. Only the period from two hours before the work shift through to two hours after the work shift is shown.
Figure 4-17. Group and individual alertness total AUCs for the winter drill crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily alertness AUCs relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem alertness AUCs during day shift (■) and night shift (■). Asterisks indicate a significant difference between shifts (*p<0.05, **p<0.01, ***p<0.005, †p<0.001).
4.3.8 Alertness in relation to phase

Figure 4-18 shows the relationship between aMT6s acrophase and the total, first half of shift and second half of shift AUCs for the winter drill crew. There were no significant correlations between aMT6s acrophase position and total AUC alertness \((r=-0.17, df=41, p>0.05)\), first half of shift AUC \((r=-0.23, df=41, p>0.05)\) and second half of shift AUC \((r=-0.10, df=41, p>0.05)\).

4.4 Spring results

4.4.1 Sample population

The mean age and number of subjects studied for the group is given in Table 4-2. All subjects were male and in good health.

Table 4-2: Mean age for the spring drill crew.

<table>
<thead>
<tr>
<th></th>
<th>Mean ± sem age (years)</th>
<th>Number in group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drill crew (spring)</td>
<td>32.6 ± 1.8</td>
<td>7</td>
</tr>
</tbody>
</table>

4.4.2 Light levels

The scotoperiod over the spring study period (provided by Bristow Helicopters, Safe Gothia) and shift pattern are shown in Figure 4-19. Light exposure during the study periods on night shift ranged between 70 and 1800 lux \((1014 ± 263 \text{ lux, mean ± sem})\) and consisted of natural and artificial light (cool white fluorescent). Exposure during the day shift ranged between 70 and 2000 lux \((1040 ± 287 \text{ lux, mean ± sem})\) and consisted of both natural and artificial light. Lighting in the accommodation was identical to that in winter (section 4.3.2).

As mentioned earlier (section 4.3.2), the crew were constantly exposed to the natural light-dark environment during their work periods.
Figure 4-18. Correlation between aMT6s acrophase and alertness for the winter drill crew.

(a) Total AUCs vs acrophase

\[ r = -0.17 \text{ df}=41 \text{ p}>0.05 \]

(b) 1st half AUCs vs acrophase

\[ r = -0.23 \text{ df}=41 \text{ p}>0.05 \]

(c) 2nd half AUCs vs acrophase

\[ r = -0.10 \text{ df}=41 \text{ p}>0.05 \]
The black bars represent the period of natural darkness with the horizontal square brackets showing the range of sunset and sunrise times.

### 4.4.3 6-sulphatoxymelatonin

The daily aMT6s acrophases for both crews are shown in Figure 4-20. Day one is the first day on shift and day eight is the period of rapid changeover. The day shift acrophases phase delayed slightly, from a position of 0544h ± 0.47 hours (mean ± sem) to 0654h ± 0.56 hours respectively, in line with the delay of the sleep and work periods. However, following the rapid change over (day 8), there was a significant (p<0.05) phase advance from the day shift position to 0051h ± 1.70 hours (mean ± sem) by day 12. The relation between the acrophase positions and the shift pattern is shown in Figure 4-21. Although the acrophase position phase advanced towards the rest period it was still present throughout the entire work period.

### 4.4.4 Subjective sleep

The average sleep chart for the winter drill crew is shown in Figure 4-22. There were no significant (p>0.05) day of shift effects on sleep onset and offset during either day shift or night shift.

Figure 4-23 shows the group and individual sleep latencies. There were no significant (p>0.05) day of shift effects during the whole fortnight, day shift or night shift. There was an overall significantly (p<0.05) longer sleep latency during day shift compared to night shift for the group. Sleep latency was significantly longer during day shift compared to night shift in subjects S16-HB (p<0.05) and S18-AD (p<0.01).

Figure 4-24 shows the group and individual sleep durations. There were no significant (p>0.05) day of shift effects during the whole fortnight, day shift or night shift. There was no overall significant difference (p>0.05) between day shift and
Figure 4-20. aMT6s acrophase positions for the spring drill crew.

Mean ± sem daily aMT6s acrophase positions (●). Where error bars are not visible they are encompassed in the symbol.
Figure 4-21. aMT6s acrophases in relation to the shift schedule for the spring drill crew.

Mean ± sem daily aMT6s acrophase positions (●) superimposed on the shift schedule. Crossed bars represent time off the installation, black bars represent free time and white bars represent the work shift period.
Figure 4-22. Daily subjective sleep patterns for the spring drill crew.

Crossed bars represent no data, black bars represent sleep and white bars represent the time awake. Sleep onset and offset times are means and the error bars are standard error of the means.
Figure 4-23. Daily subjective sleep latencies for the spring drill crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily subjective sleep latencies relative to individual means during day shift (○) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem subjective latencies during day shift (■) and night shift (■). The asterisks indicate a significant difference between shifts (*p<0.05, **p<0.01).
Figure 4-24. Daily subjective sleep durations for the spring drill crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily subjective sleep durations relative to individual means during day shift (○) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem subjective durations during day shift (■) and night shift (■).
night shift for the group. There were no significant differences (p>0.05) between day shift and night shift in individuals.

Figure 4-25 shows the group and individual sleep efficiencies. There were no significant (p>0.05) day of shift effects during the whole fortnight, day shift or night shift. There was an overall significantly (p<0.05) higher sleep efficiency during day shift compared to night shift for the group. Sleep efficiency was significantly higher on night shift compared to day shift in subject S16-HB (p<0.01).

Figure 4-26 shows the group and individual sleep qualities. There were no significant (p>0.05) day of shift effects during the whole fortnight, day shift or night shift. However, during day shift there was a trend for increasing sleep quality from the start to the end of the shift. There was no overall significant difference (p>0.05) between day shift and night shift for the group. There were no significant differences (p>0.05) between day shift and night shift in individuals.

In order to examine the differences in sleep efficiency more closely the total duration of mid-sleep awakenings was also assessed. Figure 4-27 shows the group and individual duration of awakenings for the winter crew. There were no significant (p>0.05) day of shift effects during the whole fortnight, day shift or night shift. There was no overall significant difference (p>0.05) between day shift and night shift for the group. Total duration of awakenings was significantly longer during night shift compared to day shift in subject S18-AD (p<0.05).

4.4.5 Objective sleep - actigraphy

There were no significant (p>0.05) day of shift effects on sleep onset and offset during either day shift or night shift. Figure 4-28 shows the group and individual sleep latencies. There were no significant (p>0.05) day of shift effects during the whole fortnight, day shift or night shift. There was an overall significantly (p<0.05) longer sleep latency during day shift compared to night shift for the group. There were no significant differences (p>0.05) between day shift and night shift in individuals.

Figure 4-29 shows the group and individual sleep durations. There were no significant (p>0.05) day of shift effects during the whole fortnight, day shift or night shift. There was no overall significant difference (p>0.05) between day shift and
Figure 4-25. Daily subjective sleep efficiencies for the spring drill crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily subjective sleep efficiency relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem subjective efficiency during day shift (■) and night shift (■). Asterisk indicates significant difference between shifts (*p<0.01).
Figure 4-26. Daily subjective sleep qualities for the spring drill crew.

(a) Mean of all subjects

(b) Shift mean for each subject

(a) Mean ± sem daily subjective sleep quality relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem subjective quality during day shift (●) and night shift (■).
Figure 4-27. Daily subjective durations of awakenings for the spring drill crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily subjective total duration of awakenings relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem subjective duration of awakenings during day shift (■) and night shift (■). Asterisk indicates a significant difference between shifts (*p<0.05).
Figure 4-28. Daily objective sleep latencies for the spring drill crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily objective sleep latencies relative to individual means during day shift (○) and night shift (■). Zero on the y-axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem objective latencies during day shift (■) and night shift (■).
Figure 4-29. Daily objective sleep durations for the spring drill crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily objective sleep durations relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem objective durations during day shift (●) and night shift (■). Asterisk indicates a significant difference between shifts (*p<0.05).
night shift for the group. Sleep duration was significantly longer on day shift compared to night shift in subject S9-AD (p<0.05).

Figure 4-30 shows the group and individual sleep efficiencies. There were no significant (p>0.05) day of shift effects during the whole fortnight, day shift or night shift. However, during day shift there was a trend for higher sleep efficiency at the start of the shift compared to the remainder of the shift. There was no overall significant difference (p>0.05) between day shift and night shift for the group. Sleep efficiency was significantly higher on day shift compared to night shift in subject S9-AD (p<0.05).

4.4.6 Sleep parameters in relation to phase

Figure 4-31 shows the relationship between aMT6s acrophase and the subjective sleep parameters for the spring drill crew during night shift. There was no significant correlation between aMT6s acrophase position and sleep latency (r=0.05, df=21, p>0.05), duration (r=-0.16, df=21, p>0.05), efficiency (r=-0.07, df=21, p>0.05) or quality (r=-0.37, df=21, p>0.05).

Figure 4-32 shows the relationship between aMT6s acrophase and the objective sleep parameters for the spring drill crew during night shift. There was no significant correlation between aMT6s acrophase position and sleep latency (r=-0.25, df=21, p>0.05), duration (r=-0.05, df=21, p>0.05) or efficiency (r=-0.24, df=21, p>0.05).

4.4.7 Alertness

Two examples of alertness patterns over the work period for the spring drill crew are shown in Figures 4-33 and 4-34. Figure 4-35 shows the group and individual alertness total AUCs for the spring drill crew over the work period. There were no significant (p>0.05) day of shift effects when examining the whole fortnight or day shift alone. However there was a significant day of shift effect during night shift (p<0.005), with the alertness on day 9 being significantly (p<0.05) lower than the remaining days of the shift apart from day 12. There was no overall significant difference (p>0.05) between day shift and night shift for the group. There were no significant differences (p>0.05) between day shift and night shift for individuals.
Figure 4-30. Daily objective sleep efficiencies for the spring drill crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily objective sleep efficiency relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem objective efficiency during day shift (■) and night shift (■). Asterisk indicates significant difference between shifts (*p<0.05).
Figure 4-31. Correlation between aMT6s acrophase and subjective sleep parameters for the spring drill crew.

(a) Sleep latency

![Graph showing correlation between sleep latency and aMT6s acrophase.]

$r=0.05, df=21, p>0.05$

(b) Sleep duration

![Graph showing correlation between sleep duration and aMT6s acrophase.]

$r=-0.16, df=21, p>0.05$

(c) Sleep efficiency

![Graph showing correlation between sleep efficiency and aMT6s acrophase.]

$r=-0.07, df=21, p>0.05$

(d) Sleep quality

![Graph showing correlation between sleep quality and aMT6s acrophase.]

$r=-0.37, df=21, p>0.05$
Figure 4-32. Correlation between aMT6s acrophase and objective sleep parameters for the spring drill crew.

(a) Sleep latency
\[ r = -0.25, \text{df} = 21, p > 0.05 \]

(b) Sleep duration
\[ r = -0.05, \text{df} = 21, p > 0.05 \]

(c) Sleep efficiency
\[ r = -0.24, \text{df} = 21, p > 0.05 \]
Subjective alertness on day shift (●) and night shift (■) for subject S17-RC. Time is relative to the centre of the work shift. Only the period from two hours before the work shift through to two hours after the work shift is shown.
Figure 4-34. Subjective alertness for subject S9-AD.

Subjective alertness on day shift (●) and night shift (■) for subject S9-AD. Time is relative to the centre of the work shift. Only the period from two hours before the work shift through to two hours after the work shift is shown.
Figure 4-35. Group and individual alertness total AUCs for the spring drill crew.

(a) Mean of all subjects

(b) Shift means for each subject

(a) Mean ± sem daily alertness AUCs relative to individual means during day shift (●) and night shift (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem alertness AUCs during day shift (■) and night shift (■).
4.4.8 Alertness in relation to phase

Figure 4-36 shows the relationship between aMT6s acrophase and the total, first half of shift and second half of shift AUCs for the spring drill crew. There were no significant correlations between aMT6s acrophase position and total AUC alertness ($r=-0.24$, df=22, p>0.05), first half of shift AUC ($r=-0.12$, df=22, p>0.05) and second half of shift AUC ($r=-0.32$, df=22, p>0.05).

4.5 Comparison between winter and spring

4.5.1 Subjects

There was no significant difference (p>0.05) between the ages of the winter and spring crews assessed by Student's t test. Both groups had a matched distribution of individual job types.

4.5.2 6-sulphatoxymelatonin

The aMT6s acrophases for both groups are shown in Figure 4-37. There were no significant differences (p>0.05) between the day shift acrophases of each group, both phase delaying to the same degree. The spring crew acrophases were significantly phase advanced (p<0.05) from those of the winter crew during days 11 to 14.

4.5.3 Sleep

The daily subjective and objective sleep latencies, durations and efficiencies for both groups are shown in Figures 4-38, 4-39 and 4-40 respectively. There were no significant differences (p>0.05) in sleep latency between groups either subjectively or objectively. There was a significant difference in subjective sleep duration between the groups on day 10, where the spring crew showed a significantly (p<0.05) longer sleep duration than the winter crew. No other significant differences in sleep duration were observed between the groups. There was a significant difference in subjective sleep efficiency between the groups on day 7, with a significantly (p<0.05) higher efficiency seen for the spring crew. No other significant differences in sleep efficiency were observed between the groups. However, there was a trend for higher sleep efficiency in the spring crew compared to the winter crew on both day and night shift.
Figure 4-36. Correlation between aMT6s acrophase and alertness for the spring drill crew.

(a) Total AUCs vs acrophase

(b) 1st half AUCs vs acrophase

(c) 2nd half AUCs vs acrophase
Figure 4-37. Daily aMT6s acrophase positions for the spring and winter drill crews.

Mean ± sem daily aMT6s acrophase positions for the spring (●) and winter (■) drill crews. Where error bars are not visible they are encompassed in the symbol.
Figure 4-38. Daily subjective and objective sleep latencies for the winter and spring drill crews.

Mean ± sem daily sleep latencies for the winter (■) and spring (■) drill crews.
Figure 4-39. Daily subjective and objective sleep durations for the winter and spring drill crews.

(a) Subjective duration

(b) Objective duration

Mean ± sem daily sleep durations for the winter (■) and spring (■) drill crews. Asterisk indicates a significant difference between crews (*p<0.05).
Figure 4-40. Daily subjective and objective sleep efficiencies for the winter and spring drill crews.

Mean ± sem daily sleep efficiencies for the winter (■) and spring (■) drill crews. Asterisk indicates a significant difference between crews (*p<0.05).
4.5.4 Alertness

The daily total alertness AUCs for both groups are shown in Figure 4-41. Alertness was significantly (p<0.05) higher for the spring crew than the winter crew on days 10 and 14. No other significant differences were observed. However, there was a trend for higher alertness in the spring crew compared to the winter crew during night shift.

4.6 Comparison between subjective and objective sleep

Figure 4-42 shows the subjective and objective sleep latency, duration and efficiency for the individuals in the winter drill crew on day shift and night shift. There was no overall significant difference between subjective and objective measurements of sleep latency during either day shift (p>0.05) or night shift (p>0.05). One subject (S6-SF) showed significantly longer latency objectively during both day shift (p<0.05) and night shift (p<0.05) than subjectively, while subject S15-JE showed a significantly longer latency subjectively than objectively but only on night shift (p<0.05). Sleep duration was shown to be overall significantly longer subjectively than objectively during day shift (p<0.001) and night shift (p<0.001). All subjects indicated a significantly (p<0.05) longer duration subjectively than objectively on both shifts except subject S6-SF, who had very little objective day shift data, S8-BM who had very little objective night shift data and S14-RD, who showed no significant difference in duration during day shift. Sleep efficiency was also shown to be overall significantly higher subjectively than objectively during day shift (p<0.001) and night shift (p<0.001). All subjects indicated a significantly (p<0.05) higher efficiency subjectively than objectively on both shifts except subject S6-SF, who had very little objective day shift data, S8-BM who had very little objective night shift data and S14-RD, who showed no significant difference in efficiency during day shift.

Figures 4-43, 4-44 and 4-45 show the correlation between the subjective and objective sleep parameters during the whole fortnight, the day shift alone and the night shift alone. There was no correlation between subjective and objective sleep latency for any of the three periods (r=0.02 to 0.09, df=31 to 66, p>0.05). There was a positive correlation between subjective and objective sleep duration during the whole fortnight (r=0.28, df=57, p<0.05) and during night shift alone (r=0.48, df=31,
Mean ± sem daily total alertness AUCs for the winter (■) and spring (■) drill crews. Asterisks indicate a significant difference between crews (*p<0.05).
Figure 4-42. Individual subjective and objective sleep parameters for the winter drill crew.

(a) Sleep Latency

(b) Sleep duration

(c) Sleep efficiency

Mean ± sem individual subjective (solid bars) and objective (crossed bars) (a) sleep latency, (b) sleep duration and (c) sleep efficiency on day shift (red) and night shift (blue). Asterisks represent a significant difference between subjective and objective measurements during the same shift (*p<0.05, **p<0.01, ***p<0.005, †p<0.001).
Figure 4-43. Correlation between subjective and objective sleep latency for the winter drill crew.

(a) Entire two weeks
\[ r = 0.06 \text{ df}=66 \text{ p}>0.05 \]

(b) Day shift
\[ r = 0.09 \text{ df}=31 \text{ p}>0.05 \]

(c) Night shift
\[ r = 0.02 \text{ df}=34 \text{ p}>0.05 \]
Figure 4-44. Correlation between subjective and objective sleep duration for the winter drill crew.

(a) Entire two weeks
\[ r = 0.28 \text{ df}=57 \text{ p}<0.05 \]

(b) Day shift
\[ r = 0.00 \text{ df}=25 \text{ p}>0.05 \]

(c) Night shift
\[ r = 0.48 \text{ df}=31 \text{ p}<0.01 \]
Figure 4-45. Correlation between subjective and objective sleep efficiency for the winter drill crew.

(a) Entire two weeks

(b) Day shift

(c) Night shift

Subjective sleep efficiency (%) vs. Objective sleep efficiency (%)
p<0.01), with an increase in subjective duration corresponding to an increase in objective duration. There was no correlation between subjective and objective duration on day shift (r=0, df=25, p>0.05). There was no correlation between subjective and objective sleep efficiency for any of the three periods (r=0.05 to 0.27, df=25 to 57, p>0.05).

Figure 4-46 shows the subjective and objective sleep latency, duration and efficiency for the individuals in the spring drill crew on day shift and night shift. There was no overall significant difference between subjective and objective measurements of sleep latency during either day shift (p>0.05) or night shift (p>0.05). One subject (S16-HB) showed significantly longer latency objectively during night shift (p<0.05) than subjectively, while subject S17-RC showed a significantly longer latency subjectively than objectively but only on day shift (p<0.05). Sleep duration was shown to be overall significantly longer subjectively than objectively during day shift (p<0.001) and night shift (p<0.05). All subjects indicated a significantly (p<0.05) longer duration subjectively than objectively on both shifts except subject S10-DM, who showed no significance during night shift and S17-RC, who showed no significance during night shift. Sleep efficiency was also shown to be overall significantly higher subjectively than objectively during day shift (p<0.001) and night shift (p<0.05). All subjects indicated a significantly (p<0.05) higher efficiency subjectively than objectively on both shifts except subject S18-AD, who showed no significance during day shift.

Figures 4-47, 4-48 and 4-49 show the correlation between the subjective and objective sleep parameters during the whole fortnight, the day shift alone and the night shift alone. There was a positive correlation between subjective and objective sleep latency during the whole fortnight (r=0.32, df=63, p<0.01) and during day shift alone (r=0.55, df=28, p<0.01), with an increase in subjective latency corresponding to an increase in objective latency. There was no correlation between subjective and objective latency on night shift (r=-0.02, df=34, p>0.05). There was a positive correlation between subjective and objective sleep duration during the whole fortnight (r=0.66, df=61, p<0.001), day shift alone (r=0.66, df=28, p<0.001) and during night shift alone (r=0.67, df=32, p<0.001), with an increase in subjective duration
Figure 4-46. Individual subjective and objective sleep parameters for the spring drill crew.

(a) Sleep latency

(b) Sleep duration

(c) Sleep efficiency

Mean ± sem individual subjective (solid bars) and objective (crossed bars) (a) sleep latency, (b) sleep duration and (c) sleep efficiency on day shift (red) and night shift (blue). Asterisks represent a significant difference between subjective and objective measurements during the same shift (*p<0.05, **p<0.01, ***p<0.005, *p<0.001).
Figure 4-47. Correlation between subjective and objective sleep latency for the spring drill crew.

(a) Entire two weeks

\[ r = 0.32 \text{ df=63 p}<0.01 \]

(b) Day shift

\[ r = 0.55 \text{ df=28 p}<0.01 \]

(c) Night shift

\[ r = -0.02 \text{ df=34 p}>0.05 \]
Figure 4-48. Correlation between subjective and objective sleep duration for the spring drill crew.

(a) Entire two weeks

Subjective sleep duration (hours)

Objective sleep duration (hours)

r = 0.66 df=61 p<0.001

(b) Day shift

Subjective sleep duration (hours)

Objective sleep duration (hours)

r = 0.66 df=28 p<0.001

(c) Night shift

Subjective sleep duration (hours)

Objective sleep duration (hours)

r = 0.67 df=32 p<0.001
Figure 4-49. Correlation between subjective and objective sleep efficiency for the spring drill crew.

(a) Entire two weeks

(Subjective sleep efficiency vs. Objective sleep efficiency)

Subjective sleep efficiency (%)  

Objective sleep efficiency (%)  

\[ r = -0.15 \text{ df}=62 \text{ p}>0.05 \]

(b) Day shift  

(Subjective sleep efficiency vs. Objective sleep efficiency)

Subjective sleep efficiency (%)  

Objective sleep efficiency (%)  

\[ r = 0.03 \text{ df}=28 \text{ p}>0.05 \]

(c) Night shift  

(Subjective sleep efficiency vs. Objective sleep efficiency)

Subjective sleep efficiency (%)  

Objective sleep efficiency (%)  

\[ r = -0.25 \text{ df}=33 \text{ p}>0.05 \]
corresponding to an increase in objective duration. There was no correlation between subjective and objective sleep efficiency for any of the three periods ($r=-0.25$ to $0.15$, $df=28$ to $62$, $p>0.05$).

Further analysis of sleep onset times, offset times and the duration of mid-sleep awakenings was performed to assess what factor was creating the differences in sleep duration and efficiency. Figures 4-50 and 4-51 show the individual sleep onset and offset times during day shift and night for the winter and spring crews respectively. In the winter crew only one subject (S6-SF) showed a significant difference, with objective sleep onset being significantly ($p<0.05$) later than subjectively during day shift. There was no overall significant difference ($p>0.05$) between subjective and objective parameters in this crew. In the spring crew, subject S16-HB showed a significantly later sleep onset during night shift objectively than subjectively ($p<0.05$), subjects S9-AD and S10-DM showed significantly later sleep offsets during day shift objectively than subjectively ($p<0.05$), while subject S17-RC showed a significantly later sleep offset during night shift objectively than subjectively ($p<0.01$). There was no overall significant difference ($p>0.05$) between subjective and objective parameters in this crew.

Figure 4-52 shows the individual total duration of awakenings during day shift and night shift sleep periods for the winter and spring crews. In both crews, all subjects who had both subjective and objective data showed significantly ($p<0.05$) larger duration objectively apart from one subject (S14-RD) who showed no differences. Objective duration of awakenings was overall significantly higher ($p<0.01$) than subjective duration for both crews. Figures 4-53 and 4-54 show the correlation between subjective and objective total duration of awakenings during the whole fortnight, the day shift alone and the night shift alone for the winter crew and spring crew respectively. For both crews there were no correlations between subjective and objective durations during either the whole fortnight ($r=0.14$, $0.08$; $df=56$, $62$; $p<0.05$), day shift ($r=0.04$, $0.22$; $df=25$, $28$; $p<0.05$) or night shift ($r=0.22$, $0.03$; $df=30$, $33$; $p<0.05$).
Figure 4-50. Individual subjective and objective sleep onsets and offsets for the winter drill crew.

(a) Sleep onsets

Day shift

Night shift

(b) Sleep offsets

Day shift

Night shift

Mean ± sem individual subjective (○) and objective (■) sleep onsets and offsets. Asterisks indicate significant differences between subjective and objective parameters (*p<0.05).
Figure 4-51. Individual subjective and objective sleep onsets and offsets for the spring drill crew.

Mean ± sem individual subjective (•) and objective (■) sleep onsets and offsets for. Asterisks indicate significant differences between subjective and objective parameters (*p<0.05, **p<0.01).
Figure 4-52. Individual subjective and objective sleep parameters for the winter and spring drill crews.

(a) Winter drill crew

(b) Spring drill crew

Mean ± sem individual subjective (solid bars) and objective (crossed bars) total duration of awakenings. Where no data is visible, duration is zero apart from S6-SF day shift and S8-BM night shift where no data is available. Asterisks indicate significant differences between shifts (*p<0.05, **p<0.01, ***p<0.005, †p<0.001).
Figure 4-53. Correlation between subjective and objective duration of awakenings for the winter drill crew.

(a) Entire two weeks

\[ r = 0.14 \text{ df}=56 \ p>0.05 \]

(b) Day shift

\[ r = 0.04 \text{ df}=25 \ p>0.05 \]

(c) Night shift

\[ r = 0.22 \text{ df}=30 \ p>0.05 \]
Figure 4-54. Correlation between subjective and objective duration of awakenings for the spring drill crew.

(a) Entire two weeks
\[ r = 0.08 \text{ df}=62 \text{ p}>0.05 \]

(b) Day shift
\[ r = 0.22 \text{ df}=28 \text{ p}>0.05 \]

(c) Night shift
\[ r = 0.03 \text{ df}=33 \text{ p}>0.05 \]
CHAPTER 5

NUTRITION STUDY
5. Nutrition study

5.1 Introduction

This study was designed to assess the postprandial response to a meal taken at midnight during a simulated night shift of a control room worker. Control room workers have a mainly sedentary job, regulating oil production parameters via computer monitors, under artificial light conditions. Therefore this particular offshore job was considered one of the easiest to simulate. The simulation was based on the first day of night shift on a fixed platform offshore, since this is the time of greatest desynchrony between endogenous circadian rhythms and the work regimen, thus providing the optimum time for the assessment of any abnormalities. This night shift was compared with a simulated day shift and a simulated night shift with bright light. It was also hoped that the study would highlight the time points of most interest during blood sampling so that future field studies could be optimised with a minimal amount of samples. The bright light treatment during the second simulated night shift was designed to both potentially phase shift circadian rhythms and also to possibly lower TAG levels (as seen by Ribeiro et al, submitted). The protocol for this study (see Appendix II) was approved by the University of Surrey’s Advisory Committee on Ethics (USACE) in advance.

5.2 Specific methodology

This study was carried out in the Clinical Investigation Unit at the University of Surrey and consisted of three legs; a simulated day shift as a control, a simulated night shift and a simulated night shift with bright light treatment. The study plan is shown in Figure 5-1. Each leg was made up of three baseline days followed by two shift days. The baseline days were designed to ensure that the subjects were all synchronised to a regular light-dark schedule. The two shifts days were designed to mimic the actual sleep-wake and light exposures patterns observed on the first two days of being offshore on a fixed oil platform. Therefore on the first day the subjects were required to rise at 0530 h (the time of rising necessary to catch a flight to the platform) and expose themselves to the natural light environment until 1300 h (the journey to the platform). The schedule then depended on whether a day shift or night

* Cool white fluorescent light positioned at approximate eye level around the unit in areas most commonly frequented by the subjects.
shift was being simulated. During the day shift subjects regularly conducted performance tests to simulate the working environment between 1300 h and 1800 h, and 0600 h and 1800 h, on test days 1 and 2 respectively. Enforced sleep periods copied those commonly taken on the platform. During each night shift subjects conducted the performance tests between 1800 h and 0600 h with enforced sleep periods again copying those on the platform. The light treatment on the second simulated night shift covered the whole of the work period (1800 h to 0600 h). A minimum gap of two weeks was used between each leg to allow the subjects to readjust to a normal routine. On each test day a pre-meal and test meal were given to the subjects and timed specifically for each particular shift's breakfast and lunch respectively. Subjects were fasted for at least six hours before the pre-meal. During this fasting period and also the blood collection period subjects only consumed water other than the set meals. Table 5-1 shows the contents of each meal.

**Table 5-1: Contents of the pre- and test meals.**

<table>
<thead>
<tr>
<th></th>
<th>Constituents</th>
<th>Energy (kJ)</th>
<th>Fat (%)</th>
<th>Protein (%)</th>
<th>CHO (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High fat pre-meal</td>
<td>2 medium eggs, 3 Gourmet Thins, 1 cup of decaffeinated coffee/tea.</td>
<td>1243</td>
<td>49</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>Test meal</td>
<td>Cheese sandwiches (3 slices white bread, butter (15g), cheddar cheese (40g)), 1 Fruesli bar, 1 glass orange juice (300ml)</td>
<td>3330</td>
<td>37</td>
<td>11</td>
<td>52</td>
</tr>
</tbody>
</table>

The following measurements were taken:

1) Three hourly urine collection during waking hours with one oversleep collection.
2) Subjective alertness rating every hour during the simulated work periods.
3) Daily sleep log.
4) Demographic details - age, height and weight.
5) Light exposure measurements.
6) Blood collection.
7) Performance tests: These were done during the simulated work periods of each shift (day shift - 0600 h to 1800 h, night shift - 1800 h to 0600 h) on the study days. The main purpose was to simulate the work of control room engineers. See section 2.8.4.
8) Subjective mood assessing cheerfulness and calmness hourly during the simulated work periods.
Figure 5-1. Nutrition study design.

LEG 1
Simulated day shift
- Baseline 1
- Baseline 2
- Baseline 3
- Shift day 1
- Shift day 2

LEG 2
Simulated night shift
- Baseline 1
- Baseline 2
- Baseline 3
- Shift day 1
- Shift day 2

LEG 3
Simulated night shift with bright light
- Baseline 1
- Baseline 2
- Baseline 3
- Shift day 1
- Shift day 2

Legend:
- Sleep period
- Natural light exposure
- Artificial light
- Bright light 1200 lux
- Pre-meal
- Test meal
- Study end
5.3 Nutrition study results

For ease of discussion, the three shifts have been abbreviated as follows; DS —
day shift, NS1 — night shift, and NS2 — night shift with bright light.
The studies were conducted during March and April.

5.3.1 Sample population

The mean age and number of subjects studied for each simulated shift is given
in Table 5-2. All subjects were male and in good health. Identical subjects were used
for all three studies. Three of the subjects were unable to take part in the final study
(NS2). The performance and mood data collected on DS and NS1 was only available
for five of the subjects due to the malfunctioning of the Psion computer for subject 6
on DS.

Table 5-2: Mean age for the simulation study subjects.

<table>
<thead>
<tr>
<th></th>
<th>Mean ± sem age (years)</th>
<th>Number in group</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS and NS1</td>
<td>30.5 ± 5.1</td>
<td>6</td>
</tr>
<tr>
<td>NS2</td>
<td>26.7 ± 2.7</td>
<td>3</td>
</tr>
</tbody>
</table>

5.3.2 Light levels

The window shutters in the clinical investigation unit were closed at all times
to avoid any natural light exposure. Normal artificial lighting in the unit, measured at
the eye level of each individual at various positions in the room, ranged between 230
and 320 lux (277 ±10 lux, mean ± sem). During NS2, bright light was measured
at a range of 1240 to 1490 lux (1368 ± 27 lux, mean ± sem).

5.3.3 6-sulphatoxymelatonin

Figure 5-2 shows the daily aMT6s acrophase positions for the subjects. The
data has been split into two charts to show the acrophases for all six subjects on DS
and NS1, and just the three that also took part in NS2. No data was available for
baseline day 1 due to urine collection commencing at wake up time of that day.

Intra-shift comparisons indicated that on DS, the acrophase position on
baseline day 3 (B3) was significantly (p<0.05) later than on study day 2 (S2). On
NS2, the acrophase position on study day 2 (S2) was significantly later than that on
Figure 5-2. Daily aMT6s acrophases during the nutrition study.

(a) All subjects (n = 6)

(b) Subjects who completed all shifts (n = 3)

Mean ± sem daily aMT6s acrophases for day shift (○), night shift (■) and night shift with bright light (◆). No data was available for baseline day 1 (B1) due to urine collection starting on the morning of that day. Baseline days are prefixed with ‘B’ and study days are prefixed with ‘S’. 
baseline day 2 (B2, p<0.01), baseline day 3 (B3, p<0.05) and study day 1 (S1, p<0.05). There were, however, no significant (p>0.05) differences between days on NS1.

Inter-shift comparisons between days indicated no significant (p>0.05) difference on baseline day 2 (B2), baseline day 3 (B3) and study day 1 (S1). However, while there was no significant difference in acrophase position on study day 2 (S2) between NS1 and NS2, the position on study day 2 (S2) was significantly (p<0.05) earlier on DS than the other two shifts.

Figure 5-3 shows the daily acrophases related to the shift schedules. All three studies displayed normal acrophases during the days leading up to study day 2 (S2), with an average (± sem) position of 0327h ± 0.49 hours on DS, 0405h ± 0.45 hours on NS1 and 0441 ± 0.53 hours on NS2. The acrophase on study day 2 (S2) of the first two shifts maintained this pattern, with only a slight phase advanced position of 0230h ± 0.69 hours on DS and phase delayed position of 0537h ± 1.22 hours on NS1. However, study day 2 (S2) of NS2 clearly indicated a phase delay to a position of 0824h ± 1.79 hours at the start of the daytime sleep period.

5.3.4 Subjective sleep

Given the short duration of each simulated shift, sleep data were of limited use in this study. The main purpose of recording sleep behaviour, therefore, was to check for any abnormalities in baseline sleep, and to compare sleep latency, duration, efficiency and quality between the first full sleep periods of each shift.

The average sleep charts for the three simulated shifts are shown in Figure 5-4. There were no significant (p<0.05) day of shift effects in sleep onset or offset between baseline days within each shift. Inter-shift comparisons between identical days indicated a significantly later sleep onset during NS2 than during DS (p<0.01) and NS (p<0.05) on baseline day 1 (B1), and DS (p<0.05) only on baseline day 2 (B2). A similar comparison for sleep offset indicated a significantly (p<0.05) later sleep offset during baseline day 3 (B3) of NS1 compared to DS.

Figure 5-5 shows the average daily sleep latencies for the group throughout the study. Also shown are the average sleep latencies for the short sleep episodes taken during the day on NS1 and NS2. Intra-shift comparisons between days for each
Figure 5-3. Daily aMT6s acrophase positions in relation to the shift patterns.

(a) Day shift (DS)

(b) Night shift (NS1)

(c) Night shift with bright light (NS2)

Mean ± sem daily aMT6s acrophases (*) in relation to the shift patterns. Black bars represent sleep periods, white bars represent awake periods, dark-shaded bars represent exposure to indoor light only, yellow bars represent bright light treatment and diagonally striped bars represent the periods before and after the study. Baseline days are prefixed with ‘B’ and study days are prefixed with ‘S’. Acrophases were calculated based on 24-hour periods from 1800h to 1800h.
Figure 5-4. Daily subjective sleep patterns during the nutrition study.

(a) Day shift (n = 6)

(b) Night shift (n = 6)

(c) Night shift + bright light (n = 3)

Crossed bars represent no data, dark shaded bars represent sleep and white bars represent the time awake. Sleep onset and offset times are means and the error bars are standard error of the means. Baseline days are prefixed with ‘B’ and study days are prefixed with ‘S’.
Figure 5-5. Daily sleep latencies during the nutrition study.

(a) Daily means for each shift

Mean ± sem daily sleep latencies for the simulated day shift (■ n = 6), night shift (■ n = 6) and night shift with bright light (■ n = 3). (b) Mean ± sem latencies for the short sleep period during study day S1. Baseline days are prefixed with ‘B’ and study days are prefixed with ‘S’.
shift indicated that sleep latency was only significantly (p<0.05) different on DS, with sleep latency on study day 2 (S2) being significantly (p<0.05) longer than the rest of the days. Inter-shift comparisons showed no significant (p>0.05) differences in sleep latency between baselines of each shift, the last sleep period of each shift, and the short sleep episodes on NS1 and NS2.

Figure 5-6 shows the average daily sleep durations for the group throughout the study. Also shown are the average sleep durations for the short sleep episodes taken during the day on NS1 and NS2. Intra-shift comparisons between days for each shift indicated that sleep duration was only significantly (p<0.001) different on DS, with sleep duration on study day 1 (S1) being significantly (p<0.05) shorter than the rest of the days. There were no significant (p>0.05) inter-shift differences in sleep duration between the last sleep period of each shift or the short sleep episodes on NS1 and NS2. However, sleep duration was overall significantly shorter on NS2 compared to NS1 (p<0.05) during the baseline days, with duration on baseline day 3 (B3) being significantly (p<0.05) longer on NS1 than NS2.

Figure 5-7 shows the average daily sleep efficiencies for the group throughout the study. Also shown are the average sleep efficiencies for the short sleep episodes taken during the day on NS1 and NS2. A significant (p<0.01) intra-shift difference in sleep efficiency between days was observed on DS, where study day 2 (S2) was significantly (p<0.05) lower than baseline days 1 (B1), 2 (B2) and 3 (B3). There were no significant (p>0.05) inter-shift differences in sleep efficiency between the last sleep period of each shift, the short sleep episodes on NS1 and NS2 or the baseline days of each shift.

Figure 5-8 shows the average daily sleep qualities for the group throughout the study. Also shown are the average sleep qualities for the short sleep episodes taken during the day on NS1 and NS2. Intra-shift comparisons between days for each shift indicated that sleep quality was significantly (p<0.05) different on DS and NS1, with sleep quality on study day 1 (S1) of each shift being significantly (p<0.05) lower than the rest of the days of DS and days B3 and S2 of NS1. There were no significant (p>0.05) inter-shift differences in sleep quality between baseline days of each shift or the short sleep episodes on NS1 and NS2. However, sleep quality was significantly
(a) Mean ± sem daily sleep durations for the simulated day shift (■ n = 6), night shift (■ n = 6) and night shift with bright light (■ n = 3). (b) Mean ± sem durations for the short sleep period during study day S1. Baseline days are prefixed with ‘B’ and study days are prefixed with ‘S’.
Figure 5-7. Daily sleep efficiencies during the nutrition study.

(a) Daily means for each shift

(b) Night shift means for short sleep

(a) Mean ± sem daily sleep efficiencies for the simulated day shift (■ n = 6), night shift (■ n = 6) and night shift with bright light (■ n = 3). (b) Mean ± sem efficiencies for the short sleep period during study day S1. Baseline days are prefixed with ‘B’ and study days are prefixed with ‘S’.
Figure 5-8. Daily sleep qualities during the nutrition study.

(a) Daily means for each shift

(b) Night shift means for short sleep

(a) Mean ± sem daily sleep qualities for the simulated day shift ( ■ n = 6), night shift ( ■ n = 6) and night shift with bright light ( ■ n = 3). (b) Mean ± sem qualities for the short sleep period during study day S1. Baseline days are prefixed with 'B' and study days are prefixed with 'S'.
(p<0.05) lower on DS compared to NS1 during the last sleep period of study day 2 (S2).

5.3.5 Alertness, cheerfulness and calmness

5.3.5.1 Alertness

Figure 5-9 shows the average relative alertness for all subjects over the simulated work period of DS and NS1, and for just the three subjects who also did NS2. Alertness was overall significantly (p<0.01) higher on DS than NS1. However, there were no overall significant (p>0.05) differences between either DS and NS2, or NS1 and NS2. There were also no significant (p>0.05) inter-shift differences between identical time points. The only significant intra-shift difference between time points was observed on NS1, where alertness at time point -4 hours (2000h) was significantly (p<0.05) greater than at time point 6 hours (0600h).

5.3.5.2 Cheerfulness

Figure 5-10 shows the average relative cheerfulness for all subjects over the simulated work period of DS and NS1, and for just the three subjects who also did NS2. Cheerfulness was overall significantly (p<0.01) higher on DS than NS1, but there were no overall significant (p>0.05) differences between either DS and NS2, or NS1 and NS2. There were no significant (p>0.05) inter-shift differences between identical time points or intra-shift differences.

5.3.5.3 Calmness

Figure 5-11 shows the average relative calmness for all subjects over the simulated work period of DS and NS1, and for just the three subjects who also did NS2. Calmness was overall significantly (p<0.01) higher on DS than NS1 and NS2, but there was no overall significant (p>0.05) difference between NS1 and NS2. The only significant (p<0.05) inter-shift differences between identical time points was observed at time point 3 hours, where DS was greater than NS1. Significant intra-shift differences between time points were observed on DS and NS1 only. On DS, calmness at time points -2 hours (1000h) and 5 hours (1700h) was significantly (p<0.05) lower than at time points -6 hours (0800h), -5 hours (0700h) and -4 hours (0600h). Calmness on NS1 was significantly lower at time points 0 hours (0000h)
Figure 5-9. Alertness over the simulated work periods.

(a) All subjects with complete data (n = 5)

(b) Subjects on all three shifts (n = 3)

Mean ± sem relative alertness during day shift (●), night shift (■) and night shift with bright light (♦).
Figure 5-10. Cheerfulness over the simulated work periods.

(a) All subjects with complete data \( (n = 5) \)

Mean ± sem relative cheerfulness during day shift (●), night shift (■) and night shift with bright light (♦).

(b) Subjects on all three shifts \( (n = 3) \)
Figure 5-11. Calmness over the simulated work periods.

(a) All subjects with complete data (n = 5)

(b) Subjects on all three shifts (n = 3)

Mean ± sem relative calmness during day shift (●), night shift (■) and night shift with bright light (◆).
and 1 hours (0100h) than at time points -6 hours (1800h), -5 hours (1900h) and -4 hours (2000h).

5.3.6 Performance

Detailed performance analysis is beyond the scope of this study. The following results indicate significant overall differences between the three shifts. The data should be treated with caution because the volunteers only practiced for one day, and recent research suggests a minimum of 12 practice sessions are required to remove the effects of learning (Defence and Environment Research Agency, unpublished).

5.3.6.1 Serial choice reaction time

a) Overall mean response time (1/100th sec)

Mean response time was overall significantly higher on DS than NS1, for both the left (p<0.005) and right (p<0.01) hand. However, DS was also significantly (p<0.01) higher than NS2 for the left hand only. There was no overall significant (p>0.05) difference between NS1 and NS2 for either hand.

b) Mean response time (1/100th sec) for correct responses

Response time was overall significantly higher on DS than NS1 (p<0.05) and NS2 (p<0.005) for the left hand, but only significantly (p<0.05) higher than NS1 for the right hand. There was no overall significant (p>0.05) difference between NS1 and NS2 for either hand.

c) Mean response time (1/100th sec) for incorrect responses

Response time was overall significantly (p<0.05) lower on DS than NS2 for the left hand, but significantly (p<0.05) lower than NS1 and NS2 for the right hand. There was no overall significant (p>0.05) difference between NS1 and NS2 for either hand.

d) Percentage trials incorrect

There were no overall significant (p>0.05) inter-shift differences for either hand. There were also no significant (p>0.05) intra-shift differences between time points for either hand.
c) Percentage trials above threshold

There were no overall significant (p>0.05) inter-shift differences for either hand. Also, no significant (p>0.05) intra-shift differences were observed between time points for either hand.

5.3.6.2 Sternberg memory search test

a) Presentation time of list in seconds

The only significant (p<0.01) overall inter-shift difference in presentation time was observed between DS and NS1 for list size 3, where DS was higher than NS1.

b) Number of true positives

The only significant (p<0.001) overall inter-shift difference in the number of true positives was observed between DS and NS2 for list size 7, where DS was higher than NS2.

c) Mean response time to true positives

The only significant (p<0.01) overall inter-shift difference in the response time to true positives was observed between DS and NS2 for list size 5, where DS was lower than NS2.

d) Number of false positives

Significant overall inter-shift differences in the number of false positives were observed for list size 1, where DS and NS2 were lower than NS1 (p<0.05), list size 3, where DS was greater than NS2 (p<0.01), and list size 7, where NS1 was greater than NS2 (p<0.05).

e) Mean response time to false positives

Significant overall inter-shift differences in the response time to false positives were observed for list size 1, where DS and NS2 were lower than NS1 (p<0.05), list size 3, where DS was greater than NS1 (p<0.05), and list size 7, where DS (p<0.001) and NS2 (p<0.05) were greater than NS1.

f) Number of true negatives

Significant overall inter-shift differences in the number of true negatives were observed for list size 3, where DS was lower than NS2 (p<0.05), and list size 5, where DS was lower than NS2 (p<0.05).
g) Mean response time to true negatives

Significant overall inter-shift differences in the response time to true negatives were observed for list size 1, where NS1 was higher than NS2 (p<0.01), list size 5, where NS1 was lower than NS2 (p<0.05), and list size 7, where DS was higher than NS1 (p<0.05).

h) Number of false negatives

Significant overall inter-shift differences in the number of false negatives were observed for list size 7, where DS was lower than NS2 (p<0.05).

i) Mean response time to false negatives

Significant overall inter-shift differences in the response time to false negatives were observed for list size 7, where DS was lower than NS2 (p<0.05).

5.3.7 Insulin

Figure 5-12 shows the average plasma insulin concentration at each time point for the subjects over each shift. The figure has been split into two charts to show the results for (a) all the subjects on DS and NS1 and (b) the three subjects who took part in the additional NS2 shift.

Comparisons between DS and NS1 for all the subjects indicated no significant differences (p>0.05) either between time points or between total AUCs. However, the profile on NS1 showed a slight, but non-significant (p>0.05), phase delay of its peak compared to that of DS.

The comparisons between DS, NS1 and NS2 for the three subjects who completed all three shifts showed much more interesting results. Firstly, the total AUCs were significantly different between each shift, with DS being significantly lower than NS1 (p<0.001) and NS2 (p<0.001), and NS1 being significantly higher than NS2 (p<0.05). Secondly, there were significant (p<0.05) inter-shift differences between identical time points as summarised in Table 5-3.
Figure 5-12. Plasma insulin concentrations following the test meal.

(a) All subjects (n=6)

Mean ± sem plasma insulin during day shift (●), night shift (■) and night shift with bright light treatment (◆).
Table 5-3: Significant (p<0.05) inter-shift differences in plasma insulin concentration.

<table>
<thead>
<tr>
<th>Time point (mins)</th>
<th>Shift comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>DS&lt;NS1, NS1&gt;NS2</td>
</tr>
<tr>
<td>45</td>
<td>DS&lt;NS1, NS1&gt;NS2</td>
</tr>
<tr>
<td>60</td>
<td>DS&lt;NS2</td>
</tr>
<tr>
<td>75</td>
<td>DS&lt;NS1</td>
</tr>
<tr>
<td>120</td>
<td>DS&lt;NS1</td>
</tr>
<tr>
<td>150</td>
<td>DS&lt;NS2</td>
</tr>
</tbody>
</table>

5.3.8 Glucose

Figure 5-13 shows the average plasma glucose concentration at each time point for the subjects over each shift. The figure has been split into two charts to show the results for (a) all the subjects on DS and NS1 and (b) the three subjects who took part in the additional NS2 shift.

Comparisons between DS and NS1 for all the subjects indicated no significant differences (p>0.05) either between time points or between total AUCs.

The comparisons between DS, NS1 and NS2 for the three subjects who completed all three shifts showed a similar pattern of results to those of plasma insulin. The total AUCs were significantly different between each shift, with DS being significantly lower than NS1 (p<0.001) and NS2 (p<0.005), and NS1 being significantly higher than NS2 (p<0.01). Secondly, there were significant (p<0.05) inter-shift differences between identical time points as summarised in Table 5-4.
Figure 5-13. Plasma glucose concentrations following the test meal.

(a) All subjects (n=6)

(b) Subjects on all three shifts (n=3)

Mean ± sem plasma glucose during day shift (●), night shift (■) and night shift with bright light treatment (♦).
Table 5-4: Significant (p<0.05) inter-shift differences in plasma glucose concentration.

<table>
<thead>
<tr>
<th>Time point (mins)</th>
<th>Shift comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>DS&lt;NS1</td>
</tr>
<tr>
<td>45</td>
<td>DS&lt;NS1, NS1&gt;NS2</td>
</tr>
<tr>
<td>60</td>
<td>DS&lt;NS1</td>
</tr>
<tr>
<td>75</td>
<td>DS&lt;NS1</td>
</tr>
<tr>
<td>90</td>
<td>DS&lt;NS1</td>
</tr>
<tr>
<td>120</td>
<td>DS&lt;NS1</td>
</tr>
</tbody>
</table>

5.3.9 NEFA

Figure 5-14 shows the average plasma NEFA concentration at each time point for the subjects over each shift. Figure 5-15 reproduces the above chart using treated data in order to de-mask the huge inter-individual differences and hence more clearly observe the differences between the shifts. Both figures have been split into two charts to show the results for (a) all the subjects on DS and NS1 and (b) the three subjects who took part in the additional NS2 shift.

Comparisons between DS and NS1 for all the subjects indicated that the total AUC for DS was significantly (p<0.05) higher than that of NS1. DS NEFA concentrations were significantly (p<0.05) lower at time point 0 minutes than on NS1, but significantly higher at time points 60, 75, 90, 120 and 150 minutes.

Comparisons of the total AUCs between DS, NS1 and NS2 for the three subjects who completed all three shifts indicated that the only significant difference occurred between DS and NS2, where DS was significantly (p<0.05) higher than NS2. Significant (p<0.05) inter-shift differences between identical time points are summarised in Table 5-5.
Figure 5-14. Plasma NEFA concentrations following the test meal.

(a) All subjects (n=6)

(b) Subjects on all three shifts (n=3)

Mean ± sem plasma NEFA during day shift (●), night shift (■) and night shift with bright light treatment (♦).
Figure 5-15. Difference from basal plasma NEFA concentrations following the test meal.

(a) All subjects (n=6)

(b) Subjects on all three shifts (n=3)

Mean ± sem difference from basal NEFA for during day shift (●), night shift (■) and night shift with bright light treatment (♦).
Table 5-5: Significant (p<0.05) inter-shift differences in plasma NEFA concentration.

<table>
<thead>
<tr>
<th>Time point (mins)</th>
<th>Shift comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>DS&lt;NS1</td>
</tr>
<tr>
<td>60</td>
<td>DS&gt;NS1</td>
</tr>
<tr>
<td>75</td>
<td>DS&gt;NS1</td>
</tr>
<tr>
<td>240</td>
<td>DS&lt;NS2</td>
</tr>
</tbody>
</table>

5.3.10 TAG

Figure 5-16 shows the average plasma TAG concentration at each time point for the subjects over each shift. Figure 5-17 reproduces the above chart using treated data in order to de-mask the huge inter-individual differences and hence more clearly observe the differences between the shifts. Both figures have been split into two charts to show the results for (a) all the subjects on DS and NS1 and (b) the three subjects who took part in the additional NS2 shift.

Comparisons between DS and NS1 for all the subjects indicated that there was no significant (p>0.05) difference between the total AUCs of each shift. However, DS TAG concentrations were significantly (p<0.05) higher at time point 360 minutes than on NS1.

Comparisons of the total AUCs between DS, NS1 and NS2 for the three subjects who completed all three shifts indicated that while there was no significant difference (p>0.05) between DS and NS1, NS2 was significantly (p>0.001) lower than DS and NS1. Significant (p<0.05) inter-shift differences between identical time points are summarised in Table 5-6.
Figure 5-16. Plasma TAG concentrations following the test meal.

(a) All subjects (n=6)

(b) Subjects on all three shifts (n=3)

Mean ± sem plasma NEFA during day shift (●), night shift (■) and night shift with bright light treatment (◆).
Figure 5-17. Difference from basal plasma TAG concentrations following the test meal.

(a) All subjects (n=6)

(b) Subjects on all three shifts (n=3)

Mean ± sem difference from basal TAG for during day shift (●), night shift (■) and night shift with bright light treatment (♦).
Table 5-6: Significant (p<0.05) inter-shift differences in plasma TAG concentration.

<table>
<thead>
<tr>
<th>Time point (mins)</th>
<th>Shift comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>DS&gt;NS2</td>
</tr>
<tr>
<td>240</td>
<td>DS&gt;NS2</td>
</tr>
<tr>
<td>300</td>
<td>DS&gt;NS2</td>
</tr>
<tr>
<td>360</td>
<td>DS&gt;NS1</td>
</tr>
</tbody>
</table>
CHAPTER 6

MELATONIN PILOT STUDY
6. Melatonin pilot study

6.1 Introduction

Anecdotal evidence suggests that the main problem offshore night workers have with their shift regimen is the slow return to a normal day pattern, when they return home in their free time. The method commonly used to overcome this problem was to drink large quantities of alcohol up until the desired bedtime. The melatonin study was designed primarily to improve night sleep, with the additional potential to increase the rate of readaptation. Therefore the treatment was administered at each subject’s bedtime. This timing also provided additional safety in case a subject was prone to excessive drowsiness following treatment. The protocol for this study (see Appendix III) was approved by the University of Surrey’s Advisory Committee on Ethics (USACE) in advance.

6.2 Specific methodology

This was a double-blind, randomised, placebo-controlled study carried out mainly when the subjects were home on leave. Table 6-1 shows the study summary. The study consisted of two legs of two weeks duration; one leg using melatonin and the other using placebo. A third leg, where subject were given no treatment, was planned but difficulties in recruiting subjects meant this was not possible. Baseline measurements were taken over the last two days on the oil installation to assess individual phase positions. Subjects were told to take the treatment (melatonin or placebo) approximately half an hour before their bedtime when at home. They were advised not to drive within five hours after administration or to drink alcohol excessively. Treatment was carried out for four consecutive days, during which time urine was not collected. Urine collection recommenced following a two-day ‘wash-out’ period after treatment. This was to ensure that the aMT6s measured in the samples was not derived from the exogenous source. The following measurements were taken according to the study summary:

1) Three to four hourly urine collections during waking hours with one over-sleep collection (⊙).

2) Subjective alertness rating at the same time as urine collection (⊙).
3) Daily sleep log (§).
4) Nap diaries (when appropriate).

Table 6-1: Melatonin study summary.

<table>
<thead>
<tr>
<th>Day</th>
<th>-2</th>
<th>-1</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine</td>
<td>◎</td>
<td>◎</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
</tr>
<tr>
<td>Alertness</td>
<td>◎</td>
<td>◎</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
</tr>
<tr>
<td>Sleep</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
<td>◎</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Days -1 and -2 are the last two days on the oil installation.

Alertness was recorded at varying times throughout the day for each individual. This meant that the data could not easily be grouped at specific time points. However, the measurements in this study were done in the subjects' free time, resulting in a high frequency of recordings per day. Therefore individual data were extrapolated between time points to give alertness readings at fixed two hour time points, from midnight to midnight of each day. Statistical analysis was then carried out as in section 2.8.1.

6.3 Pilot study results

6.3.1 Sample population

The mean age and number of subjects studied for each treatment is given in Table 6-2. All subjects were male and in good health. Only two subjects were able to take part in both treatments.

Table 6-2: Mean age for the melatonin study subjects.

<table>
<thead>
<tr>
<th></th>
<th>Mean ± sem age</th>
<th>Number in group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo Treatment</td>
<td>37.2 ± 4.4</td>
<td>5</td>
</tr>
<tr>
<td>Melatonin Treatment</td>
<td>36.4 ± 3.9</td>
<td>5</td>
</tr>
</tbody>
</table>

The studies were carried out between September and March.
6.3.2 6-sulphatoxymelatonin

The daily aMT6s acrophases for subjects on both treatments are shown in Figure 6-1. The first chart shows the mean aMT6s acrophases on the last day of night shift on the oilrig. The second chart shows the mean aMT6s acrophases on the days following treatment and a two-day wash out period. One subject in the melatonin treatment group was unable to supply enough urine samples for analysis and was thus discounted from the group data. The last day of post-treatment measurements for the melatonin treatment group yielded very little data and was discounted.

The data from the last night shift on the oilrig indicates that both the placebo and melatonin treatment groups adapted their aMT6s pattern to the night shift regimen, with acrophase positions of 1454h ± 0.6 hours (mean ± sem) and 1430h ± 1.3 hours (mean ± sem) respectively. There was no significant (p>0.05) difference between these acrophases. The post-treatment patterns suggest a return of the acrophase positions to that found in a normal light/dark environment, with a mean range of acrophases for the placebo treatment group of 0248h ± 0.3 hours to 0422h ± 0.4 hours (mean ± sem), and for the melatonin treatment group of 0312h ± 0.4 hours to 0434h ± 0.8 hours (mean ± sem). There were no significant (p>0.05) day of shift effects in either group, suggesting that the acrophases had reached a stable position. There were also no significant (p>0.05) inter-group differences between individual days and no overall significant (p>0.05) difference between the two groups.

6.3.3 Subjective sleep

The average sleep charts for both treatment groups are shown in Figure 6-2. While there were no significant (p>0.05) day of study effects for the days following night shift in either group, there was a trend for a delay in sleep offset in the placebo group from day 8 up to day 11. The onsets and offsets for both groups were not overall significantly (p>0.05) different from each other, but offset on study day 3 was significantly (p<0.05) earlier in the placebo group than the melatonin group. Further analysis of the treatment phase and post-treatment phase as separate entities indicated that offset during the treatment phase (study days 1 to 4) was significantly (p<0.05) earlier for the placebo group than the melatonin group.
Figure 6-1. Daily aMT6s acrophase position during the melatonin study.

(a) aMT6s acrophase at the end of night shift

![Graph showing aMT6s acrophase at the end of night shift.]

(b) aMT6s acrophase following treatment

![Graph showing aMT6s acrophase following treatment.]

Acrophases are mean ± sem. Not enough data were available for study day 12 in the melatonin group.
Figure 6-2. Daily subjective sleep patterns during the melatonin study.

(a) Placebo treatment (n = 5)

(b) Melatonin treatment (n = 5)

Crossed bars represent no data, black bars represent sleep and white bars represent the time awake. Sleep onset and offset times are means and the error bars are standard error of the means.
Figure 6-3 shows the mean daily sleep latencies for each group and the mean sleep latencies for the two individuals who were in both groups, during and after the treatments (study days 1 to 4 and 7 to 12 respectively). There was a significant overall day of study effect for both the placebo group (p<0.005) and the melatonin group (p<0.05), where latency was greater for the last night shift sleep (study day -1) compared to the remaining sleep periods of the study for both groups. There was no overall significant (p>0.05) difference in latency between the two groups, but latency on study day 9 in the placebo group was significantly (p<0.05) greater than on the same day in the melatonin group. Inter-shift analysis of the treatment period and post-treatment period separately indicated no significant (p>0.05) differences. However, subject MT_DG showed a significantly (p<0.01) higher latency during post-treatment on melatonin than on placebo.

Figure 6-4 shows the mean daily sleep durations for each group and the mean sleep durations for the two individuals who were in both groups, during and after the treatments. There were no significant (p>0.05) day of study effects for either treatment. There was no overall significant (p>0.05) difference in duration between the two groups, but duration on study day 3 in the placebo group was significantly (p<0.05) lower than on the same day in the melatonin group. No significant inter-group differences were observed when looking at the post-treatment period. However, the treatment period showed significantly (p<0.05) longer sleep duration in the melatonin group than the placebo group, with the two individuals who took part in both studies also showing this effect.

Figure 6-5 shows the mean daily sleep efficiencies for each group and the mean sleep durations for the two individuals who were in both groups, during and after the treatments. There were no significant (p>0.05) day of study effects for either treatment and no overall significant (p>0.05) difference in efficiency between the two groups. While there were no overall significant (p>0.05) inter-group differences during either the treatment or post-treatment periods, subject MT_TH showed a significantly higher efficiency during post-treatment under the melatonin regimen than the placebo regimen.
Figure 6-3. Daily sleep latencies during the melatonin study.

(a) All subjects

Mean ± sem daily sleep latencies relative to individual means under placebo (○) and melatonin (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem latencies under placebo (■) and melatonin (■). The asterisks indicate significant differences between treatment (* p<0.05, ** p<0.01).
Figure 6-4. Daily sleep durations during the melatonin study.

(a) All subjects

(b) Subjects who did both studies

(a) Mean ± sem daily sleep durations relative to individual means under placebo (●) and melatonin (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem durations under placebo (■) and melatonin (■). The asterisk (*) indicates a significant difference (p<0.05) between treatments.
Figure 6-5. Daily sleep efficiencies during the melatonin study.

(a) All subjects

(b) Subjects who did both studies

(a) Mean ± sem daily sleep efficiencies relative to individual means under placebo (●) and melatonin (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem efficiencies under placebo (■) and melatonin (■). The asterisk (*) indicates a significant difference (p<0.05) between treatments.
Figure 6-6 shows the mean sleep qualities for each group and the mean sleep qualities for the two individuals who were in both groups, during and after the treatments. While there were no significant \( p>0.05 \) day of shift effects for the melatonin group, there was an overall significant \( p<0.05 \) effect for the placebo group. Significant differences between days are shown in Table 6-3. There were no overall significant \( p>0.05 \) inter-group differences in sleep quality, but quality on study day 3 was significantly \( p<0.05 \) higher in the melatonin group than in the placebo group. Analysis of the treatment and post-treatment periods separately indicated no significant \( p>0.05 \) inter-group differences. However, subject MTDG exhibited a significantly \( p<0.005 \) higher sleep quality under the placebo regimen during the post-treatment period than under the melatonin regimen.

Table 6-3: Significant \( p<0.05 \) differences in sleep quality between days for the placebo treatment group.

| Day 3 | < Days 11, 12 |
| Day 4 | < Days 5, 6, 8, 9, 10, 11, 12 |
| Day 8 | < Day 10 |
| Day 12 | > Days -1, 3, 4, 5, 6, 7, 10 |

Figure 6-7 shows the individual sleep patterns for each group over the entire study, together with naps recorded after the last night shift. Visual inspection of the napping data suggests a higher frequency and duration of daytime naps, during the first 5 days after night shift (study days 1 to 5), in the melatonin group compared to the placebo group. However, one subject (TH_MT) who took part in both treatments indicated no napping on melatonin treatment but one nap of 30 minutes duration on study day 1 of placebo treatment.

6.3.4 Alertness

Figure 6-8 shows the mean alertness patterns for both groups on the last full day of night shift and the six days following treatment and washout. The data for some subjects on specific days was missing or limited and was excluded from the analysis. It should be noted that data shown over the sleep periods was calculated by extrapolation of values at either side of such periods. Thus it does not reflect an
Figure 6-6. Daily sleep qualities during the melatonin study.

(a) All subjects

(b) Subjects who did both studies

(a) Mean ± sem daily sleep qualities relative to individual under placebo (■) and melatonin (■). Zero on the y axis marks the shift mean for each individual on each shift. (b) Individual mean ± sem qualities under placebo (■) and melatonin (■). The asterisks indicate a significant difference between treatments (* p<0.05, ** p<0.005).
Figure 6-7. Individual sleep and nap charts for the melatonin study.

Placebo Group

- JC_MT
- DG_MT
- LW_MT
- TH_MT
- RP_MT

Melatonin Group

- DC_MT
- DG_MT
- LW_MT
- TH_MT
- WB_MT

Study day

Time (24h)

Crossed bars represent no data, black bars represent sleep, shaded bars represent naps and white bars represent the time awake.
Figure 6-8. Subjective alertness before and after melatonin or placebo treatment.

Mean ± sem relative alertness for the placebo group (○) and melatonin group (■). The asterisks indicate a significant difference between treatments (* p<0.05, ** p<0.01, *** p<0.001).
accurate depiction of the alertness at those times. For both groups, there was a significant time of day effect for each 24h period apart from the seventh day in the melatonin treatment group. Table 6-4 shows the significant time of day effects within each 24h period for both groups. An overall significant (p<0.05) difference between the two groups was observed on night shift (placebo group alertness greater than that of the melatonin group), day 7 (placebo group alertness lower than that of the melatonin group) and day 8 (placebo group alertness lower than that of the melatonin group). Significant (p<0.05) inter-group differences between individual time points were observed at times 0300h (p<0.05), 0400h (p<0.001) an 0500h (p<0.01) during night shift (placebo group alertness greater than melatonin group), time points 2300h (p<0.05) and 2400h (p<0.05) at the end of day 7 (placebo group alertness lower than melatonin group), and time point 2100h (p<0.05) during day 12 (placebo group alertness lower than melatonin group).

Table 6-4: Significant (p<0.05) time of day effects for alertness under placebo treatment and melatonin treatment.

<table>
<thead>
<tr>
<th>Day</th>
<th>Time points for each treatment (24h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS</td>
<td>Placebo: 18&lt;0,2,4,6, 10,12,14, 22,24</td>
</tr>
<tr>
<td></td>
<td>Melatonin: 0,2&lt;10,12,14, 4&gt;10,12,10,12&lt;22,24 14&lt;22</td>
</tr>
<tr>
<td>Day 7</td>
<td>Placebo: 6&lt;12,14,16,18, 8&lt;14,16,18, 10,12,20&gt;24, 14,16,18&gt;22,24</td>
</tr>
<tr>
<td></td>
<td>Melatonin: 8&lt;12,14,16,18,20</td>
</tr>
<tr>
<td>Day 8</td>
<td>Placebo: 0,2,4,6&lt;10,12,14,16,18,20, 10,20&gt;24, 14,16,18&gt;22,24</td>
</tr>
<tr>
<td></td>
<td>Melatonin: 24&lt;12,14,16,20</td>
</tr>
<tr>
<td>Day 9</td>
<td>Placebo: 0,2,4,6,8,24&lt;10,12,14,16,18,20</td>
</tr>
<tr>
<td></td>
<td>Melatonin: 0,2,6,24&lt;12,14,16,18, 4&lt;10,12,14,16,18,20</td>
</tr>
<tr>
<td>Day 10</td>
<td>Placebo: 0,2,4,6,8,24&lt;10,12,14,16,18,20</td>
</tr>
<tr>
<td></td>
<td>Melatonin: 0,2,4,8,20,22&lt;12,14,16,18,24&lt;12,14,16,18,20</td>
</tr>
<tr>
<td>Day 11</td>
<td>Placebo: 24&lt;12,14,16,18,20</td>
</tr>
<tr>
<td></td>
<td>Melatonin: 0&lt;12,14,16,18,20, 2&lt;12,14,16,18</td>
</tr>
<tr>
<td>Day 12</td>
<td>Placebo: 4&lt;16, 6&lt;12,14,16,18, 8&lt;12,14,16,18,18&lt;20, 7&lt;14,16,18,20, 24&lt;12,14,16,18,20,22</td>
</tr>
<tr>
<td></td>
<td>Melatonin: None</td>
</tr>
</tbody>
</table>
CHAPTER 7

DISCUSSION
7. Discussion

7.1 The Pros and Cons of running clinical studies

'To simulate or not to simulate'; not exactly the words of William Shakespeare, but a good question all the same. In our efforts to obtain the 'cleanest' results, we can be forgiven for wanting to control our experiments as tightly as possible. However, the reality of life is an uncontrolled, almost chaotic existence where every waking moment contains a deluge of experiences and stimuli influencing both our physical and mental states. To this end we can either conduct experiments in the 'real' world and try to remove the many influencing factors from the data, or we can run simulation experiments in which we remove as many of these factors as possible before and during data collection. Both methods have their benefits and problems, but combining the results of the two together can lead to some fascinating conclusions.

Starting with field studies, the author draws on his considerable experience of running studies on offshore oil rigs. There are very few other places where studies in a 'real' environment can be so controlled; a submarine, space shuttle, a research base in the Antarctic polar region or possibly a prison come to mind. The oil rigs contain what can be considered as a 'captive audience', with a large population of men and women who are confined to the limits of the platform under a strict shift system. While taking part in a study offers them some relief from their daily routine, they cannot be bound to the rules that we impose on paid volunteers. This means that compliance in such a study is solely at the discretion of the volunteer, and there is more emphasis on the investigator to maintain enthusiasm.

The intensity of the work on the platforms impacts heavily on the quantity and quality of data. Data collection occurs when the workload allows it, which at times can be infrequent and is hardly ever the same for individuals within the same team. To put this in perspective, each oil rig in the North Sea makes about one million pounds profit every hour. Thus, if every worker in a team (especially the drillers) were to stop work for a fifteen minute sample collection at the same time every two hours, then the
potential profit loss in a day would be approximately three million pounds! Multiply this up for a two-week study and it becomes obvious why such research is carried out at the convenience of the oil companies.

Probably the most important uncontrolled factor in such studies is light exposure. The discussions to follow point out the differences observed between night shift in winter and summer. However, a more immediate consideration is the changes in light exposure throughout a twenty-four hour period. The accommodation modules on the platforms have very few windows. At the end of a shift, individuals normally do not remain in the work areas for safety reasons. Therefore they go immediately to the accommodation block, where light exposure is almost entirely artificial (maximum 500 lux). Thus there is a finer degree of control over light exposure compared to a land-based shift work environment. It is far from absolute, however, and thus light measurements have to be made as often as possible within the safety limits of the installation.

Another consideration is the ability of the volunteers to set their own bedtime, and to a certain degree wake up time. The problem with this is that bedtimes could be influenced by other factors such as a good television program or a social event of some kind. However, unlike simulated studies where bedtimes are often imposed, the freedom to choose their own bedtime allows the study of sleep patterns, which is of considerable importance. Wake up times are often dictated by the work shift start time, and hence the benefit of their use is limited to the study of premature waking.

In conclusion it can be seen that while there are several problems in running a study of this kind, the resultant data depict a real work environment and are unforced in terms of the experimental protocol.

Simulation studies, conducted in purpose built investigation units, allow much greater control over environmental influences compared to field studies. Ranging from light exposure and temperature to set sleep periods, the environment can be maintained at a constant state or adjusted as necessary. The studies often involve paid volunteers or people who are very interested in the subject matter. Thus, a strict regimen of sample collection can be imposed with good compliance. In this way, data are collected at the same time points for every individual in a group and for each leg of
a study. Another benefit is that there is a better chance of determining the cause of any anomalies that may be found in the data, by consulting the records of the study for any factors, unrelated to it, that may have caused an influence.

With the benefits of a greater degree of control also come some major disadvantages. Firstly, the subjects often need a period of adjustment to their new environment, which is not part of the study. This adjustment is required because the volunteers are literally taken out of their normal lifestyle patterns, which may have unpredictable results on both the biological and mental responses of each individual. Unless a study particularly involves exercise, volunteers will often remain sedentary (sometimes necessary for a study) when they would normally be more active, and this can often lead to lethargy. There are also social factors, where by subjects might change their patterns of activity and rest as a function of the actions of their fellow volunteers.

Obviously a simulated environment is far from real life, but the benefit of having data of good quality and frequency, uninfluenced by many major and minor external factors, can certainly counter the shortcomings. In an ideal world, the best solution would be to run both a simulated study and a field study, using the data from both on which to base sound conclusions. To simulate or not to simulate? The answer is probably ‘yes’!

7.2 Baseline study I - fixed oil platforms

7.2.1 6-sulphatoxymelatonin data

The data clearly show the adaptation of the aMT6s rhythm to night shift, in all three groups studied, within the first week. The adaptation occurred by a phase delay (with one exception) of the aMT6s acrophase from the latter half of a normal night-sleep period, to a similar position in the day-sleep period of night shift. The mechanism of entrainment is unknown, but possible influencing factors include the forced reversal of the sleep/wake cycle, night time activity, meal timing and artificial light exposure at night.

Previous studies have indicated that the absence of natural light may facilitate adaptation, for example during winter in Antarctica (Midwinter and Arendt, 1991) and in light avoidance studies (Koller et al, 1994). Therefore we expected that the summer
technicians, who were exposed to a large amount of natural light, would display a slower rate of adaptation. However, in this study the presence or absence of natural bright light appears to have no effect on the rate of adaptation. A possible explanation for the adaptation observed in the summer technicians may be that the light at the start and end of the work shift is perceived as a dawn and dusk signal, resulting in a ‘skeleton’ photoperiod.

The lack of any significant difference between the two winter groups does not support the hypothesis that exercise may facilitate adaptation (Van Cauter et al, 1993; Van Reeth et al, 1994), since one group (drill crew) was considerably more active than the other (maintenance crew). However, nighttime exercise/activity must not be discounted as a possible method by which all three groups may have been entrained.

The individual who phase advanced rather than delayed was unavailable to be studied on day shift. Therefore the reason for the different direction of shift cannot be determined, although his initial phase position may have been a critical factor.

7.2.2 Subjective sleep

When studying sleep offset times and sleep duration it is important to note that unlike in many isolation experiments, the sleep on the oil installations was not taken *ad libitum*. The use of alarm clocks and the need for cleaning staff to clean rooms ensured that the workers were woken at least half an hour prior to the start of the work period. While all three groups showed a trend for earlier sleep onset and offset times at the start of the night shift, only the summer technician crew showed a significance in these parameters. This general lack of significance was backed up by the fact that there were no significant day of shift effects for sleep duration on night shift, no overall significant difference in duration between day and night shift and, unlike the research of Czeisler et al (1980), only showed a slight significant correlation between duration and phase in the summer technician group. It is possible that the fatigue resulting from twelve hours of strenuous work at the start of the night shift fortnight, when the workers had been used to two weeks of leave, may have outweighed the circadian rise in alertness and reduction in sleep tendency at night shift bed time.
Further evidence for the lack of any obvious sleep tendency reduction during the rest period of night shift can be seen in the sleep latency data, with no significant day of shift effects or differences between day shift and night shift. Only the winter technician crew showed any correlation between sleep latency and circadian phase, with increasing phase delay corresponding to a rise in latency. This might again highlight the overpowering effect of workload related fatigue on circadian sleep tendency.

When assessing sleep efficiency it is important to remember that it incorporates both sleep latency and the total duration of recorded mid-sleep awakenings. All three groups showed no overall significant difference between day shift and night shift sleep efficiency, with only the winter technicians showing significantly reduced efficiency during the first few days of night shift. However, both winter groups showed a significant correlation between circadian phase and sleep efficiency, with greater efficiency being observed following the delay of the aMT6s acrophase. This positive change in efficiency was observed even though latency in relation to phase in the winter drill crew showed no change and in the winter technician crew showed an increase with phase delay. This phenomenon was assessed further by determining the relation between phase and the daily total duration of mid-sleep awakenings. The resulting significant decrease in the duration of awakenings with a phase delay in both groups strongly suggests that this was the main factor driving the increase in sleep efficiency. Thus the ability to maintain sleep in these shift workers appears to be strongly related to circadian phase, with sleep maintenance being greatest around the time of maximal melatonin output and temperature nadir.

In all three groups there was a trend for increasing sleep quality throughout the night shift, this increase being significant in the summer technician crew. However there was no significant difference between day shift and night shift, with some individuals showing significantly higher quality on day shift to night shift while the reverse occurred in others. What must be taken into account is that the way in which subjects record their alertness can change between day shift and night shift due to the minimum of two weeks gap between each shift. The winter drill crew and summer technician crew showed a significant correlation between quality and phase, with a delay in aMT6s acrophase corresponding to an increase in sleep quality. This increase
in sleep quality when the aMT6s acrophase moves into the middle of the night shift sleep period agrees with the findings of Akerstedt et al (1993), who indicated that sleep quality was best when sleep was taken around the temperature minimum. The lack of any correlation between phase and sleep quality in the winter technician crew may also be explained by the work of Akerstedt et al (1993), who showed that there are two separate methods by which subjects may record sleep quality; either by recording sleep quality as high when sleep was deep (usually around the temperature minimum) or recording it as high when sleep was refreshing (usually around the temperature maximum).

7.2.3 Subjective alertness

The example individual alertness charts for each group generally show a sharp rise in alertness following the sleep period on day shift, which remains fairly stable throughout the work shift. However, during the first few days of night shift, alertness tends to be high at the start of the work shift (1800h) but then falls throughout the remainder of the shift over the time of the normal temperature nadir. Hence the data indicates a classic alertness circadian rhythm, with high levels of alertness over the temperature maximum (in this case during the day shift work period) and low levels over the temperature minimum (in this case during the night shift work period). The alignment of the night shift alertness pattern with that of the day shift after five to seven days indicates the adaptation of the alertness circadian rhythm along with the aMT6s rhythm. Looking at the daily mean for each group (Figures 3-19, 3-22, 3-37), there is a trend of increasing alertness up to the average night shift level by day five of night shift. This relation between circadian phase and subjective alertness, also described by Dijk et al (1992), can be seen more clearly in the scatter plots of relative alertness AUCs versus relative aMT6s acrophase position (Figures 3-23, 3-24, 3-38). The phase delay of the aMT6s acrophase correlates significantly with the increase in total alertness AUC in all three groups. Looking more closely at the data it can be seen that this correlation results from a change of alertness during the second half of the night shift. This can be explained again by considering the circadian alertness rhythm. The first half of the night shift work period occurs between 1800h and midnight; the period during which the temperature rhythm is slowly falling from its maximum and alertness...
is generally high. The second half of the night shift work period occurs between midnight and 0600h; the period during which the temperature rhythm falls rapidly to a minimum and then slowly starts to rise and alertness is at its lowest. Therefore, when the circadian system phase delays and the temperature minimum theoretically moves out of the second half of the night shift into the middle of the day in line with the aMT6s peak, the concomitant increase in alertness over the second half of the work period is observed.

An excellent example of the alignment of the day shift and night shift alertness patterns can be seen in subject S3-DT (Figure 3-18). The dip in alertness around the middle of the day shift work period reinitiates in the middle of the night shift work period several days after the start of the night shift. This dip in the middle of the day may be an example of the bimodality of circadian sleep tendency observed by Strogatz et al (1987).

The individual and overall differences between alertness on day shift and night shift indicate conflicting results, with overall higher alertness on day shift in the winter drill crew, higher alertness on night shift in the winter maintenance crew and no significant difference in the summer maintenance crew. The problem with such comparisons is identical to that mentioned earlier for sleep quality; the way in which subjects record their alertness can change between day shift and night shift due to the minimum of two weeks gap between each shift.

7.3 Baseline study II - floating drilling rig

7.3.1 6-sulphatoxymelatonin data

The data clearly indicate a seasonal variation in adaptation to night shift, with a phase advance occurring in spring compared to a lack of significant phase shift in winter. It is important to note, however, that the aMT6s acrophase is present throughout the whole night shift work period in both groups, suggesting that even the March group could not achieve full adaptation to the imposed regimen. The variation between the groups is most likely due to the differences in both the duration and intensity of natural light exposure. Sunrise during March occurs approximately two hours earlier than in November with a concomitant increase in light intensity. This early light exposure, falling mainly in the advance portion of the phase response curve
(Van Cauter et al, 1994), was sufficient to advance the melatonin rhythm in the March group. Similar results have been observed in light treatment studies on both normal day workers in temperate (Buresova et al, 1991) and polar (Broadway et al, 1987) regions.

7.3.2 Subjective sleep

Unlike the previous baseline study, both day shift and night shift sleep is displaced. The day shift work-rest pattern forces the phase delay of the sleep-wake cycle by a few hours from what would be considered a normal routine (2300h to 0700h). Considering the tendency for the human biological clock to naturally phase delay, the amount of disruption to sleep should be minimal. However, the night shift work-rest pattern requires, in the first instance, at least an eight-hour phase advance of the sleep-wake cycle from the day shift position. Hence significant disturbance in sleep parameters would be expected.

The amount of actual sleep disturbance on night shift appears to be low and season dependent. Both crews indicate no day of shift effects for sleep onset or offset and sleep quality does not significantly differ between day and night shift. However, the parameters of sleep latency, duration and efficiency show opposite results between the groups; the winter crew show significantly longer sleep duration on day shift compared to night shift with no effect in sleep latency and efficiency, while the spring crew show significantly longer latency and higher efficiency on day shift compared to night shift but with no change in sleep duration. Further analysis was performed to assess whether the duration of mid-sleep awakenings was responsible for the significant differences shown in sleep duration and efficiency, but neither crew indicated any day of shift effects nor significant differences between day shift and night shift in this parameter.

The lack of any significant correlation between the sleep parameters and aMT6s acrophase position on night shift suggests that sleep is unaffected by circadian phase position in this particular environment. Considering the difference in aMT6s acrophase position between the two crews on night shift, the lack of any significant difference in sleep parameters between the crews gives further evidence of this null effect of phase on sleep. However, the fact that neither group adapt fully into night shift...
shift may suggest that, rather than there being a lack of phase effect, sleep in both
groups may be poor throughout the shift and thus show no significant differences.
This may be supported by the fact that there is a trend for greater efficiency in the
spring crew, who adapted more closely to night shift, compared to the winter crew.

A similar consideration must be made when drawing conclusions as to the
differences between day shift and night shift. The earlier assumption that the phase
delay of the sleep-wake cycle on day shift would not cause sleep disruption may not be
true. If sleep is poor on day shift then its comparison with poor night shift sleep
would probably show no differences. Indeed, a study by Parkes (1994) comparing
onshore and offshore control-room operators indicated lower day shift sleep efficiency
but longer night shift sleep duration offshore compared to onshore.

7.3.3 Objective sleep

The lack of any major significant differences in all objective sleep parameters
studied, as well as no correlations between the parameters and aMT6s acrophase
position, further highlights the points mentioned above.

7.3.4 Subjective alertness

It is important to note that, unlike in the first baseline study on the fixed oil
platforms, there were no gaps between day shift and night shift alertness recordings.
Therefore comparisons between the two shifts can be considered more accurate than
in the previous study. The example alertness charts for the winter crew show a
marked reduction in alertness during night shift for at least the first few days compared
to day shift. This difference between shifts was found to be significant in this group,
with the trend for reduced alertness at the start of night shift being the influencing
factor. The spring crew alertness charts show very little difference between the two
shifts, with only the first day of night shift being significantly lower than the remaining
days and no overall significant difference being observed for the group. The lack of
any significant difference between the crews on night shift is unexpected, but may be
explained by the fact that raw data had to be used in the statistical analysis, resulting in
a strong influence of inter-individual differences in recording alertness.

The patterns of alertness observed during day shift in the example charts fit
well with the circadian rhythm theory of alertness in normal individuals. Following the
initial low level of alertness after the sleep period, there is a rapid rise up to the centre of the shift (1800h), which then steadily drops towards the end of the shift (0000h), in line with the theoretical temperature rhythm. During night shift the characteristic low level of alertness immediately following the sleep period is again observed. Also observed is the alertness reduction at the end of the shift (1200h), a time at which circadian theory would predict a rise in levels. A possible explanation may be that the fatigue resulting from twelve hours of work, as well as the anticipation of sleep, may cause the decrease in alertness observed.

While the spring crew examples show a rapid rise in alertness to the middle of the shift (0600h), similar to that seen on day shift, the winter crew examples show a reduced alertness amplitude. Since the spring crew alertness is higher even at the start of the night shift week, when both crews are in a similar circadian phase as assessed by aMT6s production, the differences in alertness must be due to a factor other than the endogenous alertness rhythm. Further evidence of this comes from the lack of correlation between aMT6s phase and alertness in either the winter or spring crew. No significant differences between the two crews were observed in subjective or objective sleep parameters. Hence sleep can also be ruled out as a factor. Therefore the most likely factor must be the potential alerting affects of light (Campbell and Dawson, 1990), considering that the rise in alertness is observed around the shift centre (0600h); a time at which the spring crew are exposed to natural light unlike the winter crew whose exposure occurs approximately two hours later.

7.3.5 Comparison between subjective and objective sleep

There are several problems associated with the subjective and objective (specifically actigraphic) measurement of sleep. For instance, the subjective measurement of sleep latency can be unreliable because it requires individuals to guess sleep onset time. The method of assessment employed by actigraphic measurement, namely by motor activity, can often result in the premature assumption of sleep onset in subjects who remain still in bed while reading a book for instance. Indeed, the reverse is true in subjects who move while asleep, with actigraphic measurement interpreting this movement as wakefulness. However, compared to more accurate means of sleep assessment such as polysomnography, both subjective and actigraphic
sleep measurement require little or no preparation and do not directly impose on the sleep environment. Using the two methods together it is possible to look more broadly at the changes in sleep under different shifts.

The comparisons between the two types of measurement for each crew indicate that both sleep duration and efficiency are recorded higher subjectively than objectively. However, these differences were not due to sleep latency, which showed no significant difference in either crew. Thus, further analysis of sleep onset/offset times and duration of mid-sleep awakenings was performed which indicated that either the duration of awakenings or movements during sleep were responsible for the observed lower objective duration and efficiency.

While these quantitative analyses show considerable differences between subjective and objective measurements, they give no indication of how well both measurements relate to one another. Therefore correlations between the two were performed to see if a change in one measurement was accompanied by a change in the other in the same direction. It was hoped that any changes in individual perception of sleep parameters between day shift and night shift could be elucidated. Obviously this could not be done using subjective data alone, since changes in actual sleep parameters rather than their method of assessment could not then be ruled out. Therefore a hypothesis was developed based on the following assumptions:

- the method of objective assessment remains constant over both shifts,
- the method of subjective assessment might change with different shifts,
- if no correlation is found between the two on either shift then no conclusions can be drawn,
- if subjective and objective data positively correlate during one shift but not the other then the subjective method of assessment may have changed,
- if subjective and objective data positively correlate during both shifts then the subjective method of assessment has probably not changed between the two shifts.

Based on these assumptions, sleep efficiency and the duration of mid-sleep awakenings were not used because no correlations between subjective and objective data were found in these parameters for either crew. Sleep latency was not used for the winter crew because no correlation was observed. However, for the spring crew,
subjective and objective sleep latency correlated positively during day shift but not night shift, suggesting that a change in the subjective method of assessment between the two shifts may have occurred. Since the correlation was not observed during night shift, it may be concluded that the ability to assess sleep latency was compromised during this shift. For the spring crew there was a positive correlation between subjective and objective sleep duration on both shifts, suggesting that perception of this parameter was unaffected by shift type. However, the winter crew only indicated a positive correlation in sleep duration during night shift, suggesting a change in the subjective method of assessment between the two shifts may have occurred. Since the correlation was not observed during day shift, it may be concluded that the ability to assess sleep duration was comprised during this shift.

7.4 Nutrition study

7.4.1 6-sulphatoxymelatonin data

While the main purpose of this study was to examine the post-prandial response to a test meal on a simulated night shift, it is still interesting to look at the aMT6s data in such an environment. Indeed, it is important to ensure that the data shows a similar pattern to that found on the real night shift in the earlier baseline studies (see Baseline study I - fixed oil platforms).

The first interesting feature is the slight advance of the acrophase position on study day 2 of day shift. This may be a result of the forced advance of the sleep schedule. Although this would suggest that the effect was immediate, it should be noted that the initiation of this forced pattern began with the advanced offset of sleep on study day 1, where the subjects were instructed to expose themselves to natural light as soon as they woke up.

The magnitude of the phase delay (0441 ± 0.53 hours to 0824h ± 1.79 hours) in acrophase position on study day 2, following bright light treatment, is surprisingly larger than the current view of the limits of entrainment (Wever, 1983; Klerman et al, 1996). However, this result may not be a reflection of the endogenous rhythm of melatonin as such, but rather an expression of masking, which would affect data analysis. It is quite possible that the suppression of melatonin by the bright light treatment may result in a rebound peak when the treatment was terminated. This peak
would actually occur somewhere on the downward path of the rhythm but would not be interpreted so by cosinor analysis.

The acrophase position on study day 2 of night shift without bright light showed the expected delay. Although this delay was only slight, it was significantly different from the day shift acrophase on the same day. This reinforces confidence in the simulation being close to the real environment, especially in relation to the night shift drill crew observed in Baseline Study I.

7.4.2 Subjective sleep

The subjective sleep data showed very few significant differences in sleep parameters of any consequence. This is a similar observation to that found in Baseline Study I, where the lack of sleep over the night shift resulted in increased fatigue which may have out-weighed the circadian rise in alertness and reduction in sleep tendency at night shift bed time.

One interesting observation is the significantly lower sleep quality on the last sleep period of day shift compared to that of night shift without bright light. One would expect the night shift sleep quality to be much lower. However, two main factors may be responsible for the difference observed. Firstly, the sleep period on night shift follows a 16-hour awake period, with no sleep during the night, in which performance tests were run and blood was being taken. Therefore, the resulting fatigue from this period may have resulted in a better quality daytime sleep. Secondly, the last sleep period of night shift occurs after blood collection, whereas the last sleep period of day shift occurs before blood collection. The poorer sleep quality on day shift may therefore have been as a result of anxiety about the imminent cannulation and blood collection.

7.4.3 Subjective alertness, cheerfulness and calmness

The human endogenous alertness rhythm is considered to follow closely that of the core body temperature rhythm (Monk et al 1989) which, for a person normally active between 0700h and 2300h, peaks in the evening (about 2000h) and troughs in the early morning (about 0400h) (Refinetti and Menaker, 1992). However, while the activity pattern on day shift was only an hour in advance of the ‘normal’ working
hours, the peak in alertness appears to occur as early as two hours after the middle of the work shift, a clock time of 1400h.

In contrast, the peak in alertness observed on night shift without bright light occurs two hours after the start of the shift, a clock time of 2000h, but then drops throughout the remainder of the work period. Thus, the alertness rhythm on night shift more closely matches that of the put forward by Monk et al (1989). A similar situation is observed during night shift with bright light treatment, where alertness is high at the start of the shift then drops to minimum at around 0400h before slowly starting to rise again.

The significantly higher alertness on day shift compared to night shift without bright light concurs with the work of others (Gold et al, 1992; Budnick et al, 1994). Visual inspection suggests there is very little difference in the shape of the alertness patterns between night shift and night shift with bright light. It can therefore be considered that the lack of any significant difference between night shift with bright light and day shift was probably due to an insufficient number of volunteers (n = 3) for successful statistical analysis. While the data do not agree with other studies (Campbell and Dawson, 1990) proposing an immediate alerting effect of bright light treatment, the lack of any positive effect does not rule out longer term benefits, as observed by Czeisler et al (1990).

The patterns of cheerfulness and, to a certain extent, calmness appear to match those of alertness. Apart from relatively high levels of calmness at the start of the shift, both parameters on day shift indicate an extended peak over the early afternoon. Cheerfulness and calmness during night shift without bright light are high at the start of the shift but then gradually drop reaching a minimum towards the end of the shift (approximately 0400h for both). The parameters on night shift with bright light show a similar, but more gradual, drop throughout the shift.

The statistical data indicate that night shift results in decrements of both cheerfulness and calmness. In the case of cheerfulness, it is possible that this effect may be alleviated with bright light treatment, although more data is needed to clarify this situation.
7.4.4 Performance

The main use of performance tests in this study was to simulate a work environment. Control room engineers on offshore oil rigs generally tend to work for 45 minutes to an hour before having a 10 to 15 minute break (author’s personal observations), and hence the performance test were considered adequate to simulate this type of work regimen.

The first set of data contain the results of the serial choice reaction time test. According to Folkard et al (1993a), this type of task appears to be determined endogenously, matching to some extent the rhythm of core body temperature. However, the data from this study show significantly quicker overall response time and time for correct responses on night shift, a time when body temperature is at its theoretical minimum, compared to day shift. Indeed, response time is only quicker on day shift for incorrect responses. These data suggest an improvement in performance of this task on night shift, although there was no significant difference in the percentage of incorrect responses between the shifts. One major consideration is that, apart from a one-day practice period, day shift was the first time that the volunteers had conducted the performance tests. Recent research suggests a minimum of 12 practice sessions are required to remove the effects of learning (Defence and Environment Research Agency, unpublished).

The Sternberg memory search test data show no discernible patterns of improved or detrimental performance between shifts. While many significant differences between shifts did occur, they appear to be dependant on the list size of the presentation but in no consistent manner. Further in depth analysis of these data are beyond the scope of the study.

7.4.5 Insulin, glucose, NEFA and TAG

The insulin and glucose data for the five subjects on day shift and night shift show a similar pattern to that found by Ribeiro et al (1998) after a 9-hour phase advance. The rise and fall of glucose after the test meal was accompanied by a corresponding rise and fall of insulin in response.

A more interesting result can be observed in the data for just the three subjects who completed all three legs of the study. The levels of glucose during both night
shifts were significantly higher than on day shift, particularly around the time of maximum glucose levels. Furthermore, insulin levels were also significantly elevated at a similar time, suggesting a high degree of glucose intolerance and/or insulin insensitivity during the night shift. This would agree with a previous study that showed an increase in glucose intolerance in the early morning (with a peak at 0340h) under constant glucose infusion (Van Cauter et al, 1989). The significantly lower levels of glucose and insulin during night shift with bright light, compared to the ordinary night shift, strongly suggest that treatment with bright light facilitates glucose tolerance on night shift. However, the immediate effects are not sufficient to return levels to those observed on day shift. Given the low number of subjects, the results must be treated with caution.

The NEFA response patterns to the test meal are similar to those found by Ribeiro et al (1998), with levels on night shift dropping significantly lower than on day shift. The most likely reason for the decrease on night shift may be due to the proposed circadian rhythm of NEFA, where levels are highest during the day and drop at night (Reaven et al, 1988).

While the pattern of TAG response to the test meal indicated no major significant differences between the shifts for all five subjects, visual inspection suggests the TAG response was higher on day shift than either of the night shifts. This is even clearer where the levels have been plotted relative to basal conditions (Figure 3-18). The results conflict with those found by Ribeiro et al (1998), which show elevated TAG on night shift. One interesting point, however, is that the application of bright light treatment appears to significantly reduce the levels of TAG on night shift compared to day shift and night shift without bright light. This is not obvious from the plots, but it must be remembered that the statistical analysis was carried out by repeated measures ANOVA of raw data. The difference between the two night shifts has also been observed by Ribeiro et al (submitted). However, the data must again be treated with caution, due to the limited number of volunteers for this particular part of the study.
7.5 Melatonin pilot study

7.5.1 6-sulphatoxymelatonin data

The night shift aMT6s data confirms the results from the baseline studies in that full adaptation occurs by the end of the two-week shift, with aMT6s acrophases of 145±0.6 hours (mean ± sem) and 1430±1.3 hours (mean ± sem) for the placebo and melatonin group respectively. Both groups also appear to have adapted back into a normal light-dark pattern (mean range of acrophases: - placebo group, 0248±0.3 hours to 0422±0.4 hours (mean ± sem); melatonin group, 0312±0.4 hours to 0434±0.8 hours (mean ± sem)), with no significant difference between the post-treatment days for either group. Unfortunately this rapid shift to an adapted state before the resumption of measurements does not allow for any indication of the effect of exogenous melatonin on the aMT6s rhythm adaptation rate. A two-day wash-out period was necessary since it takes roughly 48 hours to fully metabolise exogenous melatonin (based on a 2.1µg intravenous sample – Jones et al, 1969). It can be stated, however, that exogenous melatonin taken during the first four days post night shift has no detrimental effects on the aMT6s rhythm by day 7, as indicated by the lack of any significant differences between the two groups.

At this point it is worth putting forward a theory as to what is happening with the melatonin rhythm during the treatment period. On the final day of night shift, the rhythm is approximately twelve hours out of phase with its position in a normal environment, following a phase delay as indicated by the baseline studies. It can therefore be assumed that the phase response curve to melatonin (Lewy et al, 1992) is also roughly 12 hours out of phase. The melatonin treatment occurred half an hour before bedtime, at approximately 2230h when looking at the melatonin group as a whole. According to the phase response curve, on the first day of treatment a pulse at this time would be in the region that would promote a slight phase delay. This response would be greater for each consecutive day as the phase response curve phase delayed accordingly. However, the response would still be very low, even on the fourth day, considering the region of the phase response curve being hit is only just within the phase delay region. Looking at this alone it would be expected that the shift in the endogenous rhythm would be no more than an hour or so. Here again we see
the importance of natural bright light exposure. The phase response curve to light (Van Cauter et al, 1994) would also be 12 hours out of phase on the night shift. Therefore, bright light exposure during the day on returning home from night shift would again fall in the delay portion of the response curve, at a position that would result in maximum phase shifting.

In conclusion, the adaptation back into a normal home pattern following night shift was probably achieved by a phase delay in both groups, most likely because of natural light exposure. However, the melatonin treatment group may well have adapted more quickly due to the additional influence of exogenous melatonin.

7.5.2 Subjective sleep

Subjective sleep was the only measurement recorded every day throughout the whole study. This was due to the fact that it was the easiest of all measurements to take, and thus did not impinge on the lives of the volunteers too much. This was necessary to ensure maximum recruitment and compliance.

The data clearly show that treatment with exogenous melatonin results in an increase in sleep duration when given at the desired bedtime. This is in stark contrast to duration under placebo, which is initially short following night shift, and then gradually rises throughout the course of the study. The increase under melatonin treatment appears to be due to a delay in sleep offset compared to that under placebo treatment. This increase in duration agrees with previous studies on shift workers (Folkard et al, 1993) and during clinical sleep experiments (Dollins et al, 1994). While there were no significant differences in sleep onset between the two groups, visual inspection suggests that sleep onset during melatonin treatment was more stable (as observed in a blind individuals by Sarrafzadeh et al, 1990 and Folkard et al, 1990) and generally earlier than during placebo treatment. Given that there was no significant difference in sleep latency, it may be possible that during the treatment phase the desire and ability to sleep occurred earlier in the group treated with melatonin.

Another interesting point is that while sleep efficiency was not significantly different between the groups during treatment, sleep quality had a similar pattern to that of duration. Quality under melatonin treatment was relatively high (apart from one anomalous reading on study day 4) throughout the study, while under placebo
treatment was initially relatively low and then increased throughout the study. The data suggest that melatonin treatment, taken at bedtime, improves sleep quality under these conditions, and concurs with previous studies (Folkard et al, 1993; Deacon et al, 1994).

The napping behaviour during the first five days after night shift shows some interesting results. Firstly, there appear to be fewer naps under placebo than melatonin treatment. It is hard to explain why this is occurring, but it may be due to continuing high levels of melatonin in the circulation as a result of the exogenous source. Certainly exogenous melatonin given during the daytime results in fatigue and sleepiness (Dollins et al, 1993), although exogenous melatonin given at bedtime has also been shown to increase daytime alertness (MacFarlane et al, 1991). The second interesting point is that for three out of the five subjects in the melatonin group, the naps appear to occur later in the day in the latter half of the treatment period compared to immediately after night shift. Indeed, a fourth subject (DC_MT) in that group also showed this behaviour if the long nap on study day 3 could be considered more of an extended sleep period. This may be further evidence of a phase delay in the melatonin rhythm that was predicted earlier from the phase response curve, since it has been suggested that most naps occur within a 4-hour period before and after the aMT6s acrophase (Lockley et al, 1997b).

It is obvious that while there was little significant difference between the two groups for most of the sleep parameters, the few differences observed suggest an improvement in sleep under melatonin treatment. However, this improvement may be at the cost of daytime alertness in some individuals.

7.5.3 Subjective alertness

The subjective alertness data are similar to the aMT6s acrophase data in that the subjects appear to have already adapted back into a normal pattern by the time measurements were resumed. On night shift there is the characteristic rise in alertness into the middle of the night (middle of the work shift), and at home alertness rises into the middle of the day, peaking around 1700h.

The differences between the two groups in the troughs of alertness on night shift are most likely an artefact of the method of data analysis. As with the sleep
period when the subjects were at home, there were very few data points during the
time of low alertness since they occur during sleep periods, and thus data was
extrapolated to give a rough view of alertness at these times.

In conclusion, the effect of melatonin treatment on daytime alertness when at
home could not be estimated. However, the napping behaviour mentioned earlier may
be an indication of periods of low alertness.

7.6 Conclusions

The aMT6s data from the two baseline studies have shown that adaptation of
the aMT6s rhythm to night shift on offshore oil rigs can be achieved. However, the
degree and direction of adaptation appears to be dependent on the type of shift system
and, in some cases, season. The aMT6s rhythms of workers on a two-week, 1800h to
substantially 0600h night shift, adjusted to the shift regimen within 5 to 7 days by a phase delay,
independent of season. In comparison, the aMT6s rhythms of workers on a one-week, 0000h to 1200h ‘swing shift’, only partially adapted within 4 days during March by
phase advance, and showed no adaptation in November. While this display of
seasonally dependent adaptation resulted from bright light exposure, the mechanism of
the non-seasonally dependent adaptation is not clear. Strong candidates for the latter
adaptation include bright light avoidance, a forced sleep-wake cycle and night time
exercise/activity.

It has been suggested that rotating shift-workers may develop significant
abnormalities of the entero-insular axis in response to abrupt phase shifts (Lennernas
et al, 1994; Costa, 1996). These may be important in the development of diseases
such as coronary heart disease, with an increased incidence observed in shift workers
by Knutsson (1989), and non-insulin dependent diabetes mellitus (Hampton et al,
1996). The data from the nutrition study support these hypotheses to a degree, with
increased glucose intolerance observed on the night shift. However, this is
contradicted by the lack of significantly higher TAG levels on night shift, since high
levels are thought to indicate a higher risk of coronary heart disease (Frayn and
Coppack, 1992). The application of bright light during the night shift does appear to
induce a reduction in glucose intolerance and an increase in TAG clearance. This is
especially important for the health of individuals who intend to have a long-term career
in a shift work environment. Further research on this matter may help to abolish the detrimental effects of night shift on health.

The pilot melatonin study was initially intended to be run on the oil rigs, with an investigation into the use of exogenous melatonin for treating maladaptation to night shift. However, the concern shown by the oil companies over bad publicity meant that these studies could only be carried out on the volunteers at home, independent of the oil rigs. While the work was of equal importance, especially to the workers who wanted to adapt back to home life as quickly as possible, the study became more analogous to a jet-lag experiment than to shift work. The natural bright light exposure, received during the day while back home, was undoubtedly the main factor causing the rapid adaptation back to a normal pattern. However, it is important to note that the administration of melatonin at the desired bedtime did not prevent readaptation to a normal home environment. While the improvements of sleep observed under melatonin treatment would be of great benefit to the oil rig workers on night shift, the apparent increase in daytime naps does cause some concern. If these naps occur during the daytime when the workers have exposure to natural bright light, what would be the effect during the night shift work period, when only artificial light of low intensity is present? In view of the remote location and hazardous work conditions pertaining in an offshore oil rig environment, no further depreciation in alertness and performance than that already present could be tolerated.

7.7 Future work

The baseline studies have shown that two different shift systems produce remarkably dissimilar responses in the adaptation of the aMT6s rhythm to night shift work. However, the offshore oil industry has several other shift systems in operation, including a three-week night shift (1800h to 0600h) and a reversed ‘swing’ shift consisting of one week of night shift (0000h to 1200h) followed immediately by one week of day shift (1200h to 0000h). Therefore, further baseline studies could be carried out to determine any further differences in adaptation.

As part of the author’s intended research, a protocol has been written to conduct a nutrition study, similar to the simulation study reported, on an offshore oil installation. The protocol can be found in Appendix IV. Unfortunately, permission
from the oil companies to run such a study was unavailable within the research period. However, as a result of the work presented here, and that of the other work conducted in Professor Arendt's laboratory, the Health and Safety Executive have commissioned a further three years of work to study the hormone and metabolic changes of offshore oil workers on different shift systems. This work will consist of both simulated and offshore studies.

The melatonin study clearly needs to be taken further. Specifically studies need to be conducted on the night shift itself, with constant measurements of sleep and alertness, and the potential use of other measurements such as that of the cortisol circadian rhythm to gain some indication of the degree of adaptation. This may prove difficult considering the media scepticism and the medical board's concerns over melatonin treatment.
REFERENCES
References


the human circadian pacemaker independent of the timing of the sleep-wake cycle. 


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References omitted before binding:


Appendix I

Baseline Study Protocol
Protocol Submitted To Ethics

Protocol Title: Assessment of circadian and nutritional status of oil-rig shift-workers in the field.

Principal Investigator: Richard Barnes
Address: Chronobiology Laboratory
School of Biological Sciences
University of Surrey
Guildford
Surrey, GU2 5XH
Telephone/Fax no: 01483 259712

Sponsors:
Stockgrand Ltd.
School of Biological Sciences
University of Surrey
Guildford
Surrey, GU2 5XH

Shell U.K. ExPro
1, Altens Farm Road
Nigg
Aberdeen, AB9 2HY

Name of Ethics Committee: University of Surrey’s Advisory Committee on Ethics (USACE)
Address: c/o Sarah Kitchen, Secretary
Senate House
University of Surrey
Guildford
Surrey, GU2 5XH

Responsible Personnel

<table>
<thead>
<tr>
<th>Name</th>
<th>Title Designation</th>
<th>Location</th>
<th>Office Phone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mr. R. Barnes</td>
<td>Principal Investigator, PhD Student.</td>
<td>Chronobiology Laboratory, University of Surrey</td>
<td>01483 259712</td>
</tr>
<tr>
<td>2. Dr. M. J. Forbes</td>
<td>Senior Medical Advisor, Shell ExPro.</td>
<td>Shell U.K. ExPro, 1, Altens Farm Road Aberdeen</td>
<td>01224 883031</td>
</tr>
<tr>
<td>3. Mr. E. Issac</td>
<td>Medic (Shell ExPro)</td>
<td>Cormorant Alpha</td>
<td>01224 248570</td>
</tr>
<tr>
<td>4. Mr. G. Macpherson</td>
<td>Medic (Shell ExPro)</td>
<td>Cormorant Alpha</td>
<td>01224 248570</td>
</tr>
<tr>
<td>5. Mr. M. Murray</td>
<td>Medic (Shell ExPro)</td>
<td>Cormorant Alpha</td>
<td>01224 248570</td>
</tr>
<tr>
<td>6. Prof. J. Arendt</td>
<td>Principal Supervisor, Managing Director, Stockgrand Ltd.</td>
<td>Chronobiology Laboratory, University of Surrey</td>
<td>01483 259701</td>
</tr>
<tr>
<td>7. Dr. S. Deacon</td>
<td>Academic Supervisor.</td>
<td>Chronobiology Laboratory, University of Surrey</td>
<td>01483 300800 ext. 2520</td>
</tr>
</tbody>
</table>
SIGNATURE PAGE

We agree to the conditions relating to this study as set out in the above named protocol.

I acknowledge that I have read the above named protocol and agree to carry out all of the conditions set out.

<table>
<thead>
<tr>
<th>Position</th>
<th>Signature and Date</th>
<th>Print Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Investigator</td>
<td>.....................</td>
<td>.....................</td>
</tr>
<tr>
<td>Managing Director</td>
<td>.....................</td>
<td>.....................</td>
</tr>
<tr>
<td>(Stockgrand Ltd.)</td>
<td>.....................</td>
<td>.....................</td>
</tr>
<tr>
<td>Academic Supervisor</td>
<td>.....................</td>
<td>.....................</td>
</tr>
<tr>
<td>Senior Medical Adviser</td>
<td>.....................</td>
<td>.....................</td>
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<tr>
<td>(Shell UK Expro)</td>
<td>.....................</td>
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<tr>
<td>Rig Manager</td>
<td>.....................</td>
<td>.....................</td>
</tr>
<tr>
<td>OIM</td>
<td>.....................</td>
<td>.....................</td>
</tr>
<tr>
<td>Medic</td>
<td>.....................</td>
<td>.....................</td>
</tr>
</tbody>
</table>
### Protocol Synopsis

**Title**: Assessment of circadian and nutritional status of oil-rig shift-workers in the field.

**Sponsors**: Stockgrand Ltd. and Shell Expro

**Project Phase**: Preliminary evaluation of scheduling system and volunteers' diet.

**Objectives**: To investigate the circadian and nutritional status of oil-rig shift-workers in the field.

**Planned Total Sample Size**: 15+ control room operators/operation technicians.

**Subject Selection Criteria**: Control room operators and operations technicians involved in a 12-hour shift system.

**Main Measurement Parameters**: Activity via wrist activity meters, urinary 6-sulphatoxymelatonin (melatonin metabolite), urinary caffeine and light levels in the areas to which the subjects are exposed. Sleep logs, mood assessments and a general shift work and nutrition questionnaire.

**Main Parameters of Safety**: Consent of medical supervisor and oil rig safety officer.

<table>
<thead>
<tr>
<th>Title</th>
<th>Assessment of circadian and nutritional status of oil-rig shift-workers in the field.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsors</td>
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<tr>
<td>Project Phase</td>
<td>Preliminary evaluation of scheduling system and volunteers’ diet.</td>
</tr>
<tr>
<td>Objectives</td>
<td>To investigate the circadian and nutritional status of oil-rig shift-workers in the field.</td>
</tr>
<tr>
<td>Planned Total Sample Size</td>
<td>15+ control room operators/operation technicians.</td>
</tr>
<tr>
<td>Subject Selection Criteria</td>
<td>Control room operators and operations technicians involved in a 12-hour shift system.</td>
</tr>
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<td>Main Measurement Parameters</td>
<td>Activity via wrist activity meters, urinary 6-sulphatoxymelatonin (melatonin metabolite), urinary caffeine and light levels in the areas to which the subjects are exposed. Sleep logs, mood assessments and a general shift work and nutrition questionnaire.</td>
</tr>
<tr>
<td>Main Parameters of Safety</td>
<td>Consent of medical supervisor and oil rig safety officer.</td>
</tr>
</tbody>
</table>
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1. BACKGROUND AND RATIONALE

1.1. Background

Shift-work leads to forced desynchronisation of internal rhythms both from the external environment and from each other, with consequent problems of behaviour (e.g. sleep), physiology (e.g. gut function) and performance (e.g. accident rate). Similar disorganisation of daily rhythms is seen in jet-lag, the aged, some blind subjects and in certain pathological situations (e.g. delayed sleep phase insomnia). It has been suggested that rotating shift-workers may develop significant abnormalities of the entero-insular axis in response to abrupt phase shifts. These may be important in the development of diseases such as coronary heart disease, observed in shift workers by Knutsson (1989), and non-insulin dependent diabetes mellitus. Hence, many problems may arise from undergoing shift-work, both detrimental to the worker’s long term health (e.g. diabetes), short term health (e.g. industrial accident) and general well-being (e.g. fatigue and mood). Since as much as 20% of the population of developed countries are involved in shift-work (e.g. nurses, police), these problems are of considerable importance.

1.2. Rationale

The pineal hormone melatonin (Arendt, 1988) has a strongly endogenous circadian rhythm (i.e. it is internally generated and regulated by the endogenous body clock). Hence it is commonly used as a marker rhythm of circadian status. Measurement of the melatonin metabolite 6-sulphatoxymelatonin, in urine, provides a good indication of the rhythmic production of melatonin (Arendt et al., 1986; Bojkowski et al., 1987). These measurements, together with subjective assessments of mood and sleep, will provide a good indication of the ability of a shift worker to adapt to a particular shift system. Urinary caffeine will be measured to observe the use of such a psycho-stimulatory drug in shift workers. A general questionnaire concerning health, personality etc. (based on the MRC Standard Shift Work Index Questionnaire) will be used to assess the type of people the shift workers are and how they feel about their shift system, as well as their diet.

2. OBJECTIVES OF THE STUDY

To investigate the circadian and nutritional status of oil-rig shift-workers in the field. The eventual aim will be to develop treatment measures to enhance circadian adjustment, such as the use of melatonin and bright light.
3. EXPERIMENTAL DESIGN AND METHODS

3.1. Overall design

The study will take 2x2 weeks, to cover both the night-shift and day-shift of each subject involved, for each shift team.
The subjects will continue with their normal routine.

3.1.1. Sampling

Urine: Urine will be collected sequentially over 24 hour periods every 2/3 hours (7/8 hours when asleep). Ideally urine will be collected throughout the study. The investigator or medic will retrieve each total sample at the end of each collection period, measure and record the volume and aliquot 2 ml samples for freezing. The subjects are allowed to urinate in between collection periods, but this is collected in the bottles provided and the total for that period is measured.

Activity: Wrist activity meters will be worn by the subjects at all times during the study, apart from when in the shower. The meters are similar in size to a watch and will not cause any restrictions to the wearers.

Subjective sleep logs and mood assessment: Subjects will fill in subjective estimations of sleep quality, duration, latency and number and duration of wakenings after every period of sleep. Mood will be rated on visual analogue scales (see Appendix 3) at the same time as urine collection.

Questionnaire: Each subject will fill in a general questionnaire to provide information about themselves and their normal activities. (See Appendix 4)

3.2. Number and source of subjects

Potentially 15 or more subjects (control room operators/operation technicians) will be recruited on the Cormorant Alpha oil-rig.

3.3. Urine sample analysis

All the samples will be immediately frozen, and then transported back to the Chronobiology Laboratory in the School of Biological Sciences (University of Surrey), at the end of the study, for analysis. Urinary 6-sulphatoxymelatonin (melatonin metabolite) will be measured, by a specific radioimmunoassay technique, to assess circadian status. Urinary caffeine will be measured by ELISA to assess levels of intake during the day and night shifts.
4. SUBJECT SELECTION CRITERIA

4.1. Inclusion Criteria

- Aged 18 years or over.
- Able and willing to give informed written and oral consent.

4.2. Exclusion Criteria

- None

5. SCREENING PROCEDURES FOR STUDY ENTRY

5.1. Medical supervisor and safety officer consent

In this study, the volunteers are not required to undertake any activity which could be harmful to themselves. Therefore, the consent of the medical supervisor and safety officer is considered to be sufficient in addition to the volunteers informed consent.

5.2. Instructions to Subjects

See Appendix 1

6. WITHDRAWAL OF SUBJECTS FROM STUDY

Subjects have the right to withdraw from the study at any time for any reason without prejudice. The Medical Supervisor and Principle Investigator also has the right to withdraw subjects from the study in the event of concomitant illness, adverse events, protocol violations, administrative reasons or other reasons.

At the time of withdraw, an explanation of why the subject is withdrawing from the study will be determined as completely as possible. However, the subject is not obliged to give a reason for withdrawing from the study.
7. REFERENCES

APPENDIX 1
Subject information sheet

Please read this information sheet carefully before you make up your mind about taking part in this study.
Ask for an explanation of anything which is not clear to you.

If you have read and understood the information sheet and decide to take part in the study, you will be asked to sign a consent form which says that you are entering the trial voluntarily but are free to withdraw at any time. It also says that you have had an explanation of the study and that you understood that explanation.

Why am I doing the study?

I am a PhD student studying the effects of shift-work on sleep, mood and general health. Shift-work results in a mismatch between internal biological rhythms and the external environmental and behavioural time cues (such as the light-dark cycle, meal times, imposed sleep-wake cycle etc.). A similar occurrence is experienced in the jet lag state. Your body can normally adjust to such changes in the environment, but this process usually takes several days for full adaption. The resulting desynchronisation can result in fatigue, sleeplessness, reduced performance, lowered mood, indigestion etc.

Eventually the aim is to help alleviate some or all of these problems allowing greater comfort and well-being in your work, leisure and sleep. This initial, ‘baseline’ phase will assess your ability to adapt to a particular shift schedule.

What the trial involves

This trial has been reviewed by an independent Ethics Committee which had no objections to its taking place.

Procedures:

Pre-study

Your date of birth, sex, height, weight and race will be recorded, all of which will remain confidential.
You will be given the opportunity to familiarise yourself with the equipment you will be using in the trial.

**During the study**

You will be asked to continue your daily work, leisure and sleep routine.

Your general activity and rest will be measured by an activity meter worn on the wrist. This device is very similar to a watch, and should cause no undue restrictions.

Urine samples are required every 2-3 hours (as assessed by the principal investigator). Plastic containers will be provided for urine collection. A *urine sample must be given at the end of each 2-3 hour collection period and the time noted*. You may go to the toilet within each period, but any additional urine must also be collected in the same plastic container for that period. At the end of each period the container will be taken by the nurse or investigator and replaced for the next session. Samples are not required every 2-3 hours throughout your sleep period, but a sample must be given when you get up and the time noted. Any *urine collected during the sleep period must be stored in the containers provided and mixed with the sample obtained upon rising*. Small samples will be taken from the urine and analysed for a specific marker of biological rhythms. Caffeine levels will also be measured to look at tea/coffee/cola consumption during the day. All *urine must be collected in the containers provided and stored until retrieval*.

Your mood will be measured on visual analogue scales every 2-3 hours, at the same time as urine collection. These are simple linear scales which only take approximately 1 minute to complete. You are asked how you currently feel about various things. For example, you will be asked to rate your alertness as follows:

```
Very alert | ----------- | Very drowsy
```

The middle of the line represents a feeling halfway between the two extremes. Position a cross at any point along the line: the further to the right the more alert you feel, the further to the left the more drowsy you feel.
At some point during the study (convenient to yourself) you will be required to fill in a shift work and nutrition questionnaire. This will ask you about the type of person you are, how you feel about your shift system, your daily eating habits etc. All the information you give will be kept in the strictest confidence.

Rights of the Subject

You are asked to take part in this trial voluntarily. You are free to withdraw from the trial at any time and the medical supervisor or principal investigator is free to withdraw you for medical or administrative reasons, or protocol violations.

Confidentiality

All information which you give or which is collected about you will be treated as highly confidential. None of the documents reporting the trial will identify you by name. If the results are published in medical journals, your privacy will be maintained.

The results obtained in this study may be valuable in the development of treatments of potential benefit to yourself and others.
APPENDIX 2

VOLUNTEERS CONSENT FORM

I, the undersigned, voluntarily agree to take part in the study STOCK/95/SHELL 1.

I have been given a full explanation by the scientific investigators of the nature, purpose and likely duration of the study and what I will be expected to do.

I have been given the opportunity to question the investigators on all aspects of the study, and have understood the advice and information given as a result.

I agree to comply with any instruction given to me during the study and to co-operate fully with all the study staff, informing them immediately of any problems that may have arisen.

All documentation held on a volunteer is in the strictest confidence and complies with the Data Protection Act (1984). I agree that I will not seek to restrict the use to which the results of the study may be put.

I understand that I am free to withdraw from the study at any time without needing to justify my decision and without prejudice.

I confirm that I have read and understood the above and freely consent to participating in this study. I have been given adequate time to consider my participation and agree to comply with the instructions and restrictions of the study.

If you wish to discuss any aspects of this study contact Richard Barnes on 01483 259712.

Name of volunteer ........................................
(BLOCK CAPITALS)

Signature of volunteer ........................................

Date ........................................

I confirm that I have explained the nature and purpose of the above trial.

Name of Principal Investigator ........................................
(BLOCK CAPITALS)

Signature ........................................

Date ........................................
# SLEEP LOG
Cormorant Alpha Circadian Rhythm Studies

<table>
<thead>
<tr>
<th>Subject Name :</th>
<th>Date :</th>
<th>Time :</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Time of going to bed :</th>
<th>Started trying to sleep at :</th>
<th>Estimated time taken to fall asleep (mins) :</th>
<th>Estimated number of night awakenings :</th>
<th>Estimated total time of awakenings (mins) :</th>
<th>Time of waking up :</th>
<th>Time of getting out of bed :</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>How rested do you feel after sleep?</th>
<th>How would you rate your overall sleep quality?</th>
</tr>
</thead>
<tbody>
<tr>
<td>well rested</td>
<td>extremely good</td>
</tr>
</tbody>
</table>
### MOOD AND ALERTNESS ASSESSMENT

Cormorant Alpha Circadian Rhythm Studies

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Very drowsy</th>
<th>Very alert</th>
</tr>
</thead>
<tbody>
<tr>
<td>_____________</td>
<td>_____</td>
<td></td>
<td></td>
</tr>
<tr>
<td>_____________</td>
<td>_____</td>
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<td>_____________</td>
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<td>_____________</td>
<td>_____</td>
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<td></td>
</tr>
</tbody>
</table>
APPENDIX 4
SHIFT-WORK STUDY QUESTIONNAIRE

'Oil rig name here'

PRINCIPAL INVESTIGATOR : RICHARD BARNES

MEDICAL SUPERVISOR : DR. M. J. FORBES

Subject Name :

Please note that any information you provide in the questionnaire will be treated in the strictest confidence and will not be divulged to anyone. No individual will be identified in connection with any of the research findings.

The Chronobiology Laboratory
School of Biological Sciences
University of Surrey
Guildford
Surrey GU2 5XH
1. Your General Biographical Information

Please answer the following questions as accurately as possible. Please note that the information you give will be treated in strictest confidence.

1.1. Today’s Date: ____________________________

1.2. Date of birth: __________ Weight: ________ Height: ________

1.3. Ethnic origin:  
   - Caucasian  
   - African  
   - Oriental  
   - Asian  
   - Other (please specify)  

Your Domestic Situation

1.4. Are you:  
   (tick one)  
   - (a) Married/Living with a partner  
   - (b) Separated/Divorced  
   - (c) Widowed  
   - (d) Single  

1.5. How long have you worked in your present shift system? _____ years _____ months

1.6. How long altogether have you been working shifts? _____ years _____ months

1.7. If you have taken a career break (or breaks), how long was it for in total? _____ years _____ months

Your Shift Details

1.8. On average, how many nights do you work per year? _____

1.9. All other things being equal, would you prefer to give up working shifts and get a day-time job without shifts? (Circle one)  
   
<table>
<thead>
<tr>
<th>Definitely not</th>
<th>Probably not</th>
<th>Maybe</th>
<th>Probably yes</th>
<th>Definitely yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

1.10. What are the three main advantages of your shift system for you?

   (a) ____________________________________________

   (b) ____________________________________________

   (c) ____________________________________________
1.11. What are the three main disadvantages of your shift system for you?

(a) _________________________________________________

(b) _________________________________________________

(c) _________________________________________________

1.12. Do you feel that overall the advantages of your shift system outweigh the disadvantages?

<table>
<thead>
<tr>
<th>Definitely not</th>
<th>Probably not</th>
<th>Maybe</th>
<th>Probably yes</th>
<th>Definitely yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

1.13. In general, to what extent does working shifts cause you problems with:

<table>
<thead>
<tr>
<th>Never</th>
<th>Somewhat</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

1.14. Are you satisfied with the amount of time your shift system leaves you for:

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Somewhat</th>
<th>Very much so</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

1.15. If you were entirely free to choose the start and finish times of your shifts, what times would you choose?

<table>
<thead>
<tr>
<th>START</th>
<th>FINISH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2. Your Sleep and Fatigue

2.1. At what time do you normally fall asleep and wake up at the following points within your shift system? Please use 24h time (e.g. 22:30) or clearly indicate "am" or "pm".

<table>
<thead>
<tr>
<th></th>
<th>FALL ASLEEP</th>
<th>WAKE UP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DAY SHIFT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Before your first day shift</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Between two successive day shifts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c) After your last day shift</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NIGHT SHIFT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(d) Before your first night shift</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e) Between two successive night shifts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(f) After your last night shift</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DAY OFF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(g) Before your first day off</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(h) Between two successive days off</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) After your last day off</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.2. If you normally take a nap/naps in addition to your main sleep, either at work or at home, at what time do you take it/them?

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) On day shifts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) On night shifts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c) On days off</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.3. How many hours sleep do you feel you usually need per day, irrespective of which shift you are on?

________ hours

2.4. How do you feel about the amount of sleep you normally get?

*Circle one number for each*

<table>
<thead>
<tr>
<th></th>
<th>Nowhere near enough</th>
<th>Could do with a lot more</th>
<th>Could do with a bit more</th>
<th>Get the right amount</th>
<th>Get plenty</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Between successive day shifts</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>(b) Between successive night shifts</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>(c) Between successive days off</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
2.5. How well do you normally sleep  
(Circle one number for each)

<table>
<thead>
<tr>
<th></th>
<th>Extremely badly</th>
<th>Quite badly</th>
<th>Moderately well</th>
<th>Quite well</th>
<th>Extremely well</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Between successive day shifts</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>(b) Between successive night shifts</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>(c) Between successive days off</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

2.6. How rested do you normally feel after sleep?  
(Circle one number for each)

<table>
<thead>
<tr>
<th></th>
<th>Definitely not rested</th>
<th>Not very rested</th>
<th>Moderately rested</th>
<th>Quite rested</th>
<th>Extremely rested</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Between successive day shifts</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>(b) Between successive night shifts</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>(c) Between successive days off</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

2.7. Do you ever wake up earlier than you intended?  
(Circle one number for each)

<table>
<thead>
<tr>
<th></th>
<th>Almost never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Frequently</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Between successive day shifts</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>(b) Between successive night shifts</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>(c) Between successive days off</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

2.8. Do you have difficulty in falling asleep?  
(Circle one number for each)

<table>
<thead>
<tr>
<th></th>
<th>Almost never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Frequently</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Between successive day shifts</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>(b) Between successive night shifts</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>(c) Between successive days off</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

2.9. Do you take sleeping pills?  
(Circle one number for each)

<table>
<thead>
<tr>
<th></th>
<th>Almost never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Frequently</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Between successive day shifts</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>(b) Between successive night shifts</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>(c) Between successive days off</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
2.10. Do you use alcohol to help you to sleep between successive days off? (Circle one number for each)

<table>
<thead>
<tr>
<th></th>
<th>Almost never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Frequently</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

2.11. Do you ever feel tired on:
(a) Day shifts (Circle one number for each)
(b) Night shifts
(c) Days off

<table>
<thead>
<tr>
<th></th>
<th>Almost never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Frequently</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

2.12. The following items relate to how tired or energetic you generally feel, irrespective of whether you have had enough sleep or have been working very hard. Some people appear to “suffer” from permanent tiredness, even on rest days and holidays, while others seem to have limitless energy. Please indicate the degree to which the following statements apply to your own normal feelings.

(a) I generally feel I have plenty of energy 1 2 3 4 5
(b) I usually feel drained 1 2 3 4 5
(c) I generally feel quite active 1 2 3 4 5
(d) I feel tired most of the time 1 2 3 4 5
(e) I generally feel full of vigour 1 2 3 4 5
(f) I usually feel rather lethargic 1 2 3 4 5
(g) I generally feel alert 1 2 3 4 5
(h) I often feel exhausted 1 2 3 4 5
(i) I usually feel lively 1 2 3 4 5
(j) I feel weary much of the time 1 2 3 4 5

2.13. Do you have any other comments or observations relating to your sleep and fatigue that have not been covered in the above section? If so, please try to describe them here: -

...........................................................................................................................................................................................................................................................................................
3. Your Health and Well-Being

3.1. Please indicate how frequently you experience the following, by circling the appropriate number:

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>How often is your appetite disturbed?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b)</td>
<td>How often do you have to watch what you eat to avoid stomach upsets?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>(c)</td>
<td>How often do you feel nauseous?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>(d)</td>
<td>How often do you suffer from heartburn or stomach-ache?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>(e)</td>
<td>How often do you complain of digestion difficulties?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>(f)</td>
<td>How often do you suffer from bloated stomach or flatulence?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>(g)</td>
<td>How often do you suffer from pain in your abdomen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>(h)</td>
<td>How often do you suffer from constipation or diarrhoea?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>(i)</td>
<td>How often do you suffer from heart palpitations?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>(j)</td>
<td>How often do you suffer from aches and pains in your chest?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>(k)</td>
<td>How often do you suffer from dizziness?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>(l)</td>
<td>How often do you suffer from sudden rushes of blood to your head?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>(m)</td>
<td>Do you suffer from shortness of breath when climbing the stairs normally?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>(n)</td>
<td>How often have you been told that you have high blood pressure?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>(o)</td>
<td>Have you ever been aware of your heart beating irregularly?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>(p)</td>
<td>Do you suffer from swollen feet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>(q)</td>
<td>How often do you feel &quot;tight&quot; in your chest?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>(r)</td>
<td>Do you feel you have put on too much weight since beginning shift-work?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>(s)</td>
<td>Do you feel you have lost too much weight since beginning shift-work?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
3.2. Have you suffered from any of the following (diagnosed by your doctor)?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Before starting shift-work</th>
<th>Since starting shift-work</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Chronic back pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Gastritis, duodenitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c) Gastric or duodenal ulcer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(d) Gall stones</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e) Colitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(f) Sinusitis, tonsillitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(g) Asthma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(h) High blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) Cardiac arrhythmias</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(j) High blood cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(k) Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(l) Cystitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(m) Kidney stones</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n) Eczema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(o) Chronic anxiety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(p) Depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(q) Arthritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(r) Haemorrhoids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(s) Varicose veins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(t) Headaches</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(u) Others</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.3. Have you taken any of the following medications for prolonged periods (more than three months)?

<table>
<thead>
<tr>
<th>Medication</th>
<th>Before starting shift-work</th>
<th>Since starting shift-work</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Tranquillisers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Sleeping tablets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c) Anti-depressants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(d) Antacids (e.g. Andrew’s liver salts)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e) Antispasmodics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(f) Laxatives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(g) Drugs to control high blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(h) Diuretics</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Before starting shift-work | Since starting shift-work | Never

(i) Heart medicines
(j) Vasodilators
(k) Bronchodilators
(l) Vitamins, tonics
(m) Pain killers
(n) Steroids
(o) Anti-inflammatories (e.g. Ibuprofen)
(p) Hormones (except contraceptive pills)
(q) Others

3.4. On average, how many cigarettes have you smoked per week? .............................................. ..............................................

3.5. On average, how many units of alcohol have you drunk per week? (e.g. 1 unit = 1/2 pint lager/bitter or 1 glass of wine or 1 measure of spirit) .............................................. ..............................................

3.6. On average, how many cups of caffeinated coffee/tea/cola have you drunk each day? .............................................. ..............................................

3.7. The following questions deal with how you have felt in general over the past few weeks. Please circle the most appropriate answer for each question. Remember to concentrate on present and recent complaints, not those that you have had in the distant past.

Have you recently:

(a) been able to concentrate on what you are doing? Better than usual | Same as usual | Less than usual | Much less than usual
(b) lost much sleep over worry? Not at all | No more than usual | Rather more than usual | Much more than usual
(c) felt that you are playing a useful part in things? More so than usual | Same as usual | Less than usual | Much less than usual
(d) felt capable of making decisions about things? More so than usual | Same as usual | Less than usual | Much less than usual
(e) felt constantly under strain? Not at all | No more than usual | Rather more than usual | Much more than usual
(f) felt you could overcome your difficulties? Not at all | No more than usual | Rather more than usual | Much more than usual
3.8. Below are listed some descriptions of **symptoms of anxiety**.
Please indicate the degree to which you **generally** or **typically** experience the symptom when you are feeling anxious.

<table>
<thead>
<tr>
<th>(a)</th>
<th>I perspire</th>
<th>Not at all</th>
<th>Somewhat</th>
<th>Very much so</th>
</tr>
</thead>
<tbody>
<tr>
<td>(b)</td>
<td>My heart beats faster</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(c)</td>
<td>I worry too much over something that doesn’t really matter</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(d)</td>
<td>I feel jittery in my body</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(e)</td>
<td>I imagine terrifying scenes</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(f)</td>
<td>I get diarrhoea</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(g)</td>
<td>I can’t keep anxiety provoking pictures out of my mind</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(h)</td>
<td>I feel tense in my stomach</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(i)</td>
<td>Some unimportant thought runs through my mind and bothers me</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(j)</td>
<td>I nervously pace</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(k)</td>
<td>I feel like I am losing out on things because I can’t make up my mind soon enough</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Description</td>
<td>Not at all</td>
<td>Somewhat</td>
<td>Very much so</td>
</tr>
<tr>
<td>---</td>
<td>-------------</td>
<td>------------</td>
<td>----------</td>
<td>-------------</td>
</tr>
<tr>
<td>(l)</td>
<td>I feel physically immobilised</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(m)</td>
<td>I can't keep anxiety provoking thoughts out of my mind</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(n)</td>
<td>I find it difficult to concentrate because of uncontrollable thoughts</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
4. The type of person you are

4.1. Please tick the response for each item that best describes you.

(a) Considering only your own “feeling best" rhythm, at what time would you get up if you were entirely free to plan your day?

- 05.00 - 06.30 a.m.
- 06.30 - 07.45 a.m.
- 07.45 - 09.45 a.m.
- 09.45 - 11.00 a.m.
- 11.00 a.m. - 12.00 (noon)

(b) Considering only your own “feeling best" rhythm, at what time would you go to bed if you were entirely free to plan your evening?

- 08.00 - 09.00 p.m.
- 09.00 - 10.15 p.m.
- 10.15 p.m. - 12.30 a.m.
- 12.30 - 01.45 a.m.
- 01.45 - 03.00 a.m.

(c) Assuming normal circumstances, how easy do you find getting up in the morning?

- Not at all easy
- Slightly easy
- Fairly easy
- Very easy

(d) How alert do you feel during the first half hour after having awakened in the morning?

- Not at all alert
- Slightly alert
- Fairly alert
- Very alert

(e) During the first half hour after having awakened in the morning, how tired do you feel?

- Very tired
- Fairly tired
- Fairly refreshed
- Very refreshed

(f) You have decided to engage in some physical exercise. A friend suggests that you do this one hour twice a week and the best time for him is 7.00 - 8.00 a.m. Bearing in mind nothing else but your own “feeling best" rhythm, how do you think you would perform?

- Would be in good form
- Would be reasonable form
- Would find it difficult
- Would find it very difficult

(g) At what time in the evening do you feel tired and, as a result, in need of sleep?

- 08.00 - 09.00 p.m.
- 09.00 - 10.15 p.m.
- 10.15 p.m. - 12.30 a.m.
- 12.30 - 01.45 a.m.
- 01.45 - 03.00 a.m.

(h) You wish to be at your peak performance for a test which you know is going to be mentally exhausting and lasting for two hours. You are entirely free to plan your day, and considering only your own “feeling best" rhythm, which one of the four testing times would you choose?

- 08.00 - 10.00 a.m.
- 11.00 a.m. - 1.00 p.m.
- 03.00 - 05.00 p.m.
- 07.00 - 09.00 p.m.

(i) One hears about “morning” and “evening" types of people. Which one of these types do you consider yourself to be?

- Definitely a morning type
- More a morning than an evening type
- More an evening than a morning type
- Definitely an evening type
4.2. The following questions are concerned with your daily habits and preferences. Please indicate what you prefer to do, or can do, and not what you may be forced to do by your present work schedule or routine. Please work through the questions as quickly as possible. It is your immediate reaction to the questions that we are interested in, rather than a carefully deliberated answer. There are no "right" or "wrong" answers to any of the questions.

<p>| (a) | Do you tend to need more sleep than other people? | 1 | 2 | 3 | 4 | 5 |
| (b) | If you are feeling drowsy can you easily overcome it if you have something to do? | 1 | 2 | 3 | 4 | 5 |
| (c) | Do you find it fairly easy to get to sleep whenever you want to? | 1 | 2 | 3 | 4 | 5 |
| (d) | Can you miss out a night's sleep without too much difficulty? | 1 | 2 | 3 | 4 | 5 |
| (e) | Do you find it difficult to &quot;wake-up&quot; properly if you are awoken at an unusual time? | 1 | 2 | 3 | 4 | 5 |
| (f) | If you had to do a certain job in the middle of the night, do you think you could do it almost as easily as at a more normal time of day? | 1 | 2 | 3 | 4 | 5 |
| (g) | Do you find it easy to &quot;sleep in&quot; in the morning if you got to bed very late the previous day? | 1 | 2 | 3 | 4 | 5 |</p>
<table>
<thead>
<tr>
<th>Question</th>
<th>Almost never</th>
<th>Seldom</th>
<th>Sometimes</th>
<th>Usually</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>If you go to bed very late do you need to sleep in the following morning?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Can you easily keep alert in boring situations?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you fairly unaware as to what time it is?</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>If you are tired, do you have difficulty keeping awake even though you need to?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you enjoy working at unusual times of day or night?</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Do you feel sleepy for a while after waking in the morning?</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Do you get up later than normal when you are on holiday?</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>If you have a lot to do, can you stay up late to finish it off without feeling too tired?</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Does the time of day have a large effect on your mood and abilities?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you find it easy to work late at night as earlier in the day?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If you have to get up early one morning do you tend to feel tired all day?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you “nod-off” if you are listening to, or watching, a boring programme?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Can you easily go to sleep earlier than normal to “catch-up” on lost sleep, e.g. after several late nights?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you have no strong preference as to when you sleep?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Can you manage with only a few hours sleep each night for several days in a row without too much difficulty?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you find it fairly difficult to overcome tiredness even in a challenging situation?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Would you be just as happy to do something in the middle of the night as during the day?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you rely on an alarm clock, or someone else, to wake you up in the morning?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Question</td>
<td>Almost never</td>
<td>Seldom times</td>
<td>Usually always</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>--------------</td>
<td>--------------</td>
<td>----------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you get to sleep fairly quickly when you have gone to bed earlier than normal?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Do you go to parties, or have evenings out with friends, if you have to get up early the following morning?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Do you need a cup of coffee or tea to wake up properly after you have been asleep?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Are there particular times of day when you would avoid doing certain jobs if you could?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>If you could do so, would you rather wait for half-an-hour or so after waking in the morning before eating a large breakfast?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

4.3. Here are some questions regarding the way you behave, feel and act. Try to decide which response option represents your usual way of acting or feeling. There are no right or wrong answers to any of the questions: your immediate reaction is what we want. Please check that you have answered all the questions. (Circle one number for each).

<table>
<thead>
<tr>
<th>Question</th>
<th>Almost never</th>
<th>Quite seldom</th>
<th>Quite often</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you like plenty of excitement and bustle around you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Does your mood go up and down?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Are you rather lively?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Do you feel ‘just miserable’ for no good reason?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Do you like mixing with people?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>When you get annoyed do you need someone friendly to talk to?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Would you call yourself happy-go-lucky?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Are you troubled about feelings of guilt?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Can you let yourself go and enjoy yourself a lot at a lively party?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Would you call yourself tense or ‘highly strung’?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Do you like practical jokes?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Do you suffer from sleeplessness?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
5. NUTRITION

5.1. Please state any vigorous exercise you perform, more than three times a week, for 20 minute sessions during the following periods.

(a) Day shift ........................................
(b) Night shift ........................................
(c) On leave ...........................................

5.2. At work are you physically active for more than 4 hours per working day? (Circle one)

Yes  No

5.3. Have you noticed changes in:

(a) your body weight since working on the rig? (Circle one)

Yes  No

Please give details........................................

(b) your body shape since working on the rig? (Circle one)

Yes  No

Please give details........................................

5.4. Do you worry about your body weight? (Circle one)

Yes  No

5.5. On what days do you eat:

(Please tick the relevant box or boxes for each)

after waking and before starting work on the day shift?

after waking and before starting work on the night shift?

eat breakfast when on leave?

in the middle of your working hours on the day shift?

in the middle of your working hours on the night shift?

in the middle of the day (e.g. lunch) when on leave?

after your working hours have finished on the day shift?

after your working hours have finished on the night shift?

at the end of the day (e.g. dinner) when on leave?

before going to sleep on the day shift?

before going to sleep on the night shift?

before going to sleep (e.g. supper) when on leave?

snacks when you are on the day shift?

snacks when you are on the night shift?

snacks when on leave?
5.6. Which is the largest meal of the above on:

(a) the day shift? .................................................................
(b) the night shift? ..............................................................
(c) leave? ...........................................................................

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Frequently</th>
<th>Always</th>
</tr>
</thead>
</table>

5.7. Do you drink:
beverages containing caffeine (e.g. tea, coffee) on the day shift? 1
Which? ........................................................................
beverages containing caffeine on the night shift? 1
Which? ........................................................................
beverages containing caffeine when you are on leave? 1
Which? ........................................................................

<table>
<thead>
<tr>
<th>Caffeine containing beverages</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
</table>

5.8. Do you drink:

<table>
<thead>
<tr>
<th>Beverage</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffee</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coke/Pepsi</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet Coke/Pepsi</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot chocolate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.9. Do you drink:
beverages which do not contain caffeine on the day shift? 1
Which? ........................................................................
beverages which do not contain caffeine on the night shift? 1
Which? ........................................................................
beverages which do not contain caffeine when on leave? 1
Which? ........................................................................

<table>
<thead>
<tr>
<th>Caffeine-free beverages</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fizzy drinks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decaffeinated coffee</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decaffeinated tea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squashes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.10. Do you drink:

<table>
<thead>
<tr>
<th>Beverage</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fizzy drinks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caffeine free Coke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decaffeinated coffee</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decaffeinated tea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Squashes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5.11. Do you drink alcoholic drinks when on leave?

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Frequently</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

5.12. Do you drink:
- Beer
- Lager
- Wine
- Spirits
- Liqueurs
- Fortified wines (e.g. port)
- Others

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
</table>

5.13. On average how many units of alcohol do you drink per week when on leave?

(NB 1 unit = half pint beer or glass wine or one measure spirit)

Yes No

5.14. Do you smoke?

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
</table>

On average how many cigarettes do you smoke per day on the day shift?

On average how many cigarettes do you smoke per day on the night shift?

On average how many cigarettes do you smoke per day when on leave?

Day-Night-Leave

shift shift shift

5.15. On average when do you think you eat most food?

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
</table>

Which foods do you eat most of? (Please give details)

Why?

On average when do you think you drink the most non-alcoholic beverages?

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
</table>

Which beverage do you drink most of? (Please give details)

Why?

Yes No

5.16. Do you avoid any food items on the day shift?

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
</table>

Which food items?

Why?

Do you avoid any food items on the night shift?

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
</table>
Which food items?.................................................................

Why?..............................................................................

Do you avoid any food items when on leave? 1  2

Which food items?.................................................................

Why?..............................................................................

5.17. Do you avoid any beverages on the day shift? 1  2

Which beverages?.................................................................

Why?..............................................................................

Do you avoid any beverages on the night shift? 1  2

Which beverages?.................................................................

Why?..............................................................................

Do you avoid any beverages when on leave? 1  2

Which beverages?.................................................................

Why?..............................................................................

5.18. Are you on a diet to lose weight? 1  2

5.19. Are you on a special diet for medical reasons (e.g. allergy)? 1  2

If yes which diet are you following and for how long? ..............................................

5.20. Would you eat more given the chance on the day shift? 1  2

Which foods?.................................................................

Why?..............................................................................

Would you eat more given the chance on the night shift? 1  2
Which foods?.................................................................................................
Why?...................................................................................................................

Would you eat more given the chance when on leave? 1 2
Which foods?.................................................................................................
Why?...................................................................................................................

5.21. Would you drink more non-alcoholic beverages given the chance on the day shift? 1 2
Which drinks?.......................................................................................................
Why?...................................................................................................................

Would you drink more non-alcoholic beverages given the chance on the night shift? 1 2
Which drinks?........................................................................................................
Why?.......................................................................................................................

Would you drink more non-alcoholic beverages more given the chance when on leave? 1 2
Which drinks?........................................................................................................
Why?.......................................................................................................................

5.22. When are you most hungry on:
(a) the day shift? ............................
(b) the night shift? ............................
(c) leave? ......................................

5.23. When are you least hungry on:
(a) the day shift? ............................
(b) the night shift? ............................
(c) leave? ......................................

5.24. Given the opportunity would you eat more? .................................
Yes  No

5.25. Do you eat if you are tired? 1 2
What do you eat?................................................................................................
Why?....................................................................................................................
5.26. Do you drink if you are tired?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

What do you drink?

Why?

5.27. Do you drink beverages which contain caffeine if you are tired?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Which?

Why?

When do you consume the most caffeine containing drinks?

<table>
<thead>
<tr>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Frequently</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.28. Do you binge eat at any occasion on:

(a) the day shift?

If yes when during the day?

What?

(b) the night shift?

If yes when during the day?

What?

(c) leave?

If yes when during the day?

What?

5.29. Do you binge drink (e.g. coffee, tea, coke) at any occasion on:

(a) the day shift?

If yes when during the day?

What?

(b) the night shift?

If yes when during the day?

What?
5.30. Do you limit your food intake ever on:
   (a) the day shift?
      1  2  3  4  5
   If so, why?..............................................................
   (b) the night shift?
      1  2  3  4  5
   If so, why?..............................................................
   (c) leave?
      1  2  3  4  5
   If so, why?..............................................................

5.31. Do you prefer sweet or savoury foods given the choice?
      1  2
   Does this preference change on day, night or leave?
   If yes, how does it change?................................. Yes  No

5.32. Do you have a preference for chocolate and foods containing chocolate at any time?
      1  2
   Does this preference change on the day, night or leave?.................................
Appendix II

Nutrition Study Protocol
# PROTOCOL FOR SUBMISSION TO USACE

**Protocol Title:** Post-prandial hormone and metabolic response to a test meal on a simulated night shift.

**Principal Investigator:** Richard Barnes  
**Address:** Chronobiology Laboratory  
School of Biological Sciences  
University of Surrey  
Guildford  
Surrey, GU2 5XH  
**Telephone/Fax no:** 01483 259712

**Sponsors:** Stockgrand Ltd.  
School of Biological Sciences  
University of Surrey  
Guildford  
Surrey, GU2 5XH

**Name of Ethics Committee:** University of Surrey’s Advisory Committee on Ethics (USACE)  
**Address:** c/o Sarah Bryan, Secretary  
Senate House  
University of Surrey  
Guildford  
Surrey, GU2 5XH

## RESPONSIBLE PERSONNEL

<table>
<thead>
<tr>
<th>Name</th>
<th>Title Designation</th>
<th>Location</th>
<th>Office Phone</th>
</tr>
</thead>
</table>
| 1. Mr. R. Barnes | Principal Investigator.  
PhD Student. | Chronobiology Laboratory, University of Surrey | 01483 259712       |
| 2. Dr. J. Wright | Medical Supervisor.                | School of Biological, University of Surrey.   | 01483 300800 ext. 2515 |
| 3. Dr. S. Hampton | Collaborative nutrition investigator. | Endocrinology and Metabolism Group, University of Surrey. | 01483 259732       |
| 4. Prof. J. Arendt | Principal Supervisor.  
Managing Director, Stockgrand Ltd. | Chronobiology Laboratory, University of Surrey | 01483 300800 ext. 2504 |
<table>
<thead>
<tr>
<th>Title</th>
<th>Post-prandial hormone and metabolic response to a test meal on a simulated night shift.</th>
</tr>
</thead>
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<tr>
<td>Sponsors</td>
<td>Stockgrand Ltd.</td>
</tr>
<tr>
<td>Project Phase</td>
<td>Nutrition assessment.</td>
</tr>
<tr>
<td>Objectives</td>
<td>To determine the post-prandial hormone and metabolic response to a fixed, test meal at various intervals throughout the first night of night shift. To identify potential risk factors associated with coronary heart disease, atherosclerosis and diabetes.</td>
</tr>
<tr>
<td>Study Design</td>
<td>Control period: Meal study on a simulated day shift. Test periods: (1) Meal study on a simulated night shift. (2) Meal study on a simulated night shift with bright light treatment.</td>
</tr>
<tr>
<td>Planned Total Sample Size</td>
<td>12 volunteers recruited from University and newspaper advertisements.</td>
</tr>
<tr>
<td>Subject Selection Criteria</td>
<td>Healthy individuals.</td>
</tr>
<tr>
<td>Test meal</td>
<td>High fat pre-meal: 2 medium eggs scrambled, 3 gourmet thins and decaffeinated tea or coffee with very low fat milk. 1243kJ. Test meal: 1½ cheese sandwiches, a Fruesli bar and orange juice (300 ml). 3330kJ.</td>
</tr>
<tr>
<td>Controls</td>
<td>The same individuals repeat the study on day shift.</td>
</tr>
<tr>
<td>Main Parameters of Safety</td>
<td>Inclusion/exclusion criteria.</td>
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8. BACKGROUND AND RATIONALE

8.1. Background

Shift-work leads to forced desynchronisation of internal rhythms both from the external environment and from each other, with consequent problems of behaviour (e.g. sleep), physiology (e.g. gut function) and performance (e.g. accident rate). Similar disorganisation of daily rhythms is seen in jet-lag, the aged, some blind subjects and in certain pathological situations (e.g. delayed sleep phase insomnia). It has been suggested that rotating shift-workers may develop significant abnormalities of the entero-insular axis in response to abrupt phase shifts. These may be important in the development of diseases such as coronary heart disease (CHD), with an increased incidence observed in shift workers by Knutsson (1989), and non-insulin dependent diabetes mellitus (NIDDM) (Hampton et al., 1996).

Hence, many problems may arise from undergoing shift-work, both detrimental to the worker’s long term health (e.g. diabetes), short term health (e.g. industrial accident) and general well-being (e.g. fatigue and mood). Since as much as 20% of the population of developed countries are involved in shift-work (e.g. nurses, police) these problems are of considerable importance.

8.2. Rationale

The mechanism by which shiftwork leads to an increase in CHD and possibly NIDDM is still unclear, but there is increasing evidence that it is the response to meals at times out of phase with the body clock that may promote risk factors. If this proves to be correct then not only will problems arise at the start of a night shift, but also at the end of night shift when changing back to a normal routine (or day shift) if full adaptation has occurred.

Glucose tolerance has been shown to decrease throughout the day and into the night in normal individuals (Service et al., 1983), and it is now clear that glucose and insulin responses are modulated by circadian rhythmicity (Van Cauter et al., 1992). Other factors have also been seen to exhibit diurnal variation, such as gut hormones (e.g. glucose-dependent insulinotropic polypeptide (GIP)) and non-esterified fatty acids (NEFAs). A recent study by our group has shown significantly altered pancreatic B-cell responses and post-prandial glucose and lipid metabolism in simulated shiftwork (Hampton et al., 1996).

A predominance of small, dense LDL (LDL-III density 1.040-1.063g/ml) in plasma has been associated with a 4 to 6-fold increase in coronary heart disease risk (Griffin et al., 1994) and has been implicated in atherogenesis through its increased susceptibility to oxidative modification (Griffin et al., 1993) and selective binding to arterial proteoglycans (Anber et al., 1996). Small, dense LDL is a well established feature of an atherogenic lipoprotein phenotype, the dislipidaemia of insulin resistance, and as such is associated with the phenomenon of triglyceride intolerance, enhanced post-prandial lipaemia and reduced levels of putatively protective HDL.

This study will examine the post-prandial hormone and metabolic responses to a test meal of volunteers simulating a day shift (0600h - 1800h) and night shift (1800h - 0600h). The responses will be related to the phase position of the biological clock (as assessed by measurement of the melatonin metabolite 6-sulphatoxymelatonin in urine). Levels of insulin resistance, lipid metabolism and lipoprotein phenotype will be
monitored to identify potential risk factors associated with CHD, atherosclerosis and NIDDM. The use of bright, full spectrum light (1200 lux) will be used to assess its ability to phase shift biological rhythms in an effort to normalise the post-prandial response on night shift.

9. OBJECTIVES OF THE STUDY

- To determine the post-prandial hormone and metabolic response to a fixed, test meal on the first night of night shift.
- To identify potential risk factors associated with coronary heart disease, atherosclerosis and diabetes.
- To try and prevent the development of any abnormal response by using bright, full spectrum light (1200 lux).

10. EXPERIMENTAL DESIGN AND METHODS

10.1. Overall design

The study will involve 2 test periods and a control period of 5 days each. The control period will simulate the first 2 days of a day shift and the test periods will simulate the first 2 days of night shift with and without bright light (1200 lux) treatment. The first 3 days are baseline days when the subjects will try to sleep between 2330h and 0730h but continue normal life otherwise. The two test days for each leg will be conducted in the Clinical Investigation Unit at the University of Surrey. Circadian measurements will be conducted every day of each study period. The study design is summarised in chart 1.
10.2. Number and source of subjects

Potentially 12 subjects will be recruited from the University of Surrey and surrounding area via advertisements in the local press and on campus.

10.3. Measurements

- Urine: Urine will be collected sequentially over 24 hour periods every 3 hours (8 hours when asleep) for every study day. The subjects will measure and record the total volume of each sample and aliquot 2 ml samples for freezing. The subjects are allowed to urinate in between collection periods, but this is collected in the bottles provided and the total for that period is measured.

- Activity: Wrist activity meters will be worn by the subjects at all times during the study periods, apart from when in the shower. The meters are similar in size to a watch and will not cause any restrictions to the wearers.

- Subjective sleep logs and alertness assessment (see Appendix 4): Subjects will fill in subjective estimations of sleep quality, duration, latency and number and duration of awakenings after every period of sleep or nap. Alertness will be rated on visual analogue scales every 3 hours when awake on each study day.

- Demographic details: The age, height and weight of each subject will be recorded at the start of the first study.

- Blood: An indwelling canula will placed into an antecubital vein of each subject prior to the test meal. Two baseline blood samples will be taken at 10 and 0 min before the test meal and then further blood samples at 15, 30, 45, 60, 75, 90, 120, 150, 180, 240, 270, 300 and 360 min will be taken after the test meal. 12 ml of blood will be taken at each time point and collected into lithium/heparin tubes. Subjects will remain in the Clinical Investigation Unit during the blood collection period.

10.4. Sample analysis

10.4.1. Urine analysis

All the samples will be immediately frozen until they are ready for analysis. Urinary 6-sulphatoxymelatonin (melatonin metabolite) will be measured, by a specific radioimmunoassay technique, to assess circadian status. This metabolite is the best marker of the behaviour of the body clock in field studies, with non-invasive collection.
10.4.2. Blood analysis

All the samples will be immediately centrifuged and the plasma extracted and frozen until needed for analysis. Plasma glucose, NEFAs and TAG will be measured by standard automated enzymatic spectrophotometry. Insulin and GIP will be measured by radioimmunoassay. The proportions and plasma concentrations of the three principal LDL subclasses (LDL-I, II and III) are calculated from LDL subclass profiles generated by spectrophotometric monitoring (Griffin et al. 1990).

10.5. Test meal

Subjects will fast for at least 6 hours before the pre-meal. The contents of the pre- and test meals are as follows:

High fat pre-meal (breakfast): 2 medium eggs (scrambled), 3 Gourmet Thins (0600h or 1800h) and 1 cup of decaffeinated coffee/tea. 1243kJ 49% fat, 27% protein, 24% carbohydrate.

Test meal (lunch): Cheese sandwiches (3 slices white bread, butter (15g) and cheddar cheese (40g)), 1 Fruesli bar and 1 glass of orange juice (300 ml). 3330kJ 37% fat, 11% protein, 52% carbohydrate.

10.6. Light treatment

Bright, full spectrum light (1200 lux) will be used in leg 3 of the study between 1800h on shift day 1 and 0600h on shift day 2. This level of light exposure has been used previously in several studies approved by the USACE and has shown no harmful side effects.

11. SUBJECT SELECTION CRITERIA

11.1. Inclusion Criteria

- Males.
- Aged 18 years or over.
- Healthy individuals free of medication other than minor analgesics.
- Able and willing to give informed written and oral consent.

11.2. Exclusion criteria

- Have given blood (300 mls) within 3 months of the start of the study.
- Intend to give blood within 4 months after the study end.
- Diabetics or sufferers of gastrointestinal disorders.
12. SCREENING PROCEDURES FOR STUDY ENTRY

12.1. Instructions to Subjects

See Appendix 1

13. WITHDRAWAL OF SUBJECTS FROM STUDY

Subjects have the right to withdraw from the study at any time for any reason without prejudice. The Medical Supervisor and Principle Investigator also has the right to withdraw subjects from the study in the event of concomitant illness, adverse events, protocol violations, administrative reasons or other reasons.

At the time of withdraw, an explanation of why the subject is withdrawing from the study will be determined as completely as possible. However, the subject is not obliged to give a reason for withdrawing from the study.
14. REFERENCES


APPENDIX 1
SUBJECT INFORMATION SHEET

STUDY: SHIFTWORK/NUTR/97

There is increasing evidence that people undertaking rotating shiftwork may be more at risk of developing diseases, such as coronary heart disease and/or diabetes, than normal. The most likely cause of such diseases is the reduced hormonal response to night time meals on night shift, which has been observed in recent studies. My current research is looking at the biological effects of shiftwork on oil rig workers, but sampling in such an environment as theirs is difficult. Therefore you are asked to take part in a study designed to simulate the night shift and day shift of an offshore oil rig shift worker. Your hormonal response to food will be assessed in order to identify any differences between day and night shift. Bright light treatment will be used during one leg to assess its affect on normalising the response. The study will cover three legs of five days each, separated from each other by two weeks.

PROCEDURES:

PRE-STUDY

This trial has been reviewed by an independent Ethics Committee which had no objections to its taking place.
Your date of birth, height and weight will be recorded, all of which will remain confidential.
You will be given the opportunity to familiarise yourself with the equipment you will be using in the trial.
You must not take part in the study if you are diabetic, or have donated blood or intend to give blood within 4 months of the start or end of the study.

DURING THE STUDY

BASELINE DAYS 1, 2 & 3

Activity monitoring: Your general activity and rest will be measured by an activity meter worn on the wrist (except when washing/showering). This device is very similar to a watch, and should cause no undue restrictions.

Urine collection: Urine samples are required every 3 hours at the times given. Plastic containers will be provided for urine collection. You may go to the toilet within each period, but any additional urine must also be collected in the same plastic container for that period. Samples are not required every 3 hours throughout your sleep period, but a sample must be given when you get up and the time noted. Any urine collected during the sleep period must be stored in the containers provided and mixed with the sample obtained upon rising. At the end of each period the volume of the urine collected must be measured and recorded, and a small sample
placed in a vial provided. The vials will be frozen until they are to be analysed for a specific marker of biological rhythms.

Sleep log: You must fill out a sleep log after every sleep period which asks for bed and wake-up times, sleep quality, and number of awakenings.

**SHIFT DAYS 1 & 2**

During each simulated work shift you will be required to complete computerised performance tests. These tests require no previous experience and although the data will be used to assess performance throughout the shift, their main use is to simulate working in a control room. You will therefore be asked to do them for the whole work period (excluding frequent breaks and the lunch break). On shift day one of legs 1 and 3 (simulated night shifts) you must not eat or drink (except water) after midday. On shift day one of leg 2 (simulated day shift) you must not eat or drink (except water) after 2000h (8pm) in the evening.

Urine collection: As Baseline days.

Activity monitoring: Continuous (except during washing).

Mood assessment: Alertness, calmness and cheerfulness to be recorded at the same time as performance tests on the handheld computers provided.

Sleep log: After every sleep period.

Blood collection: You will be given a set meal at breakfast and lunch. No other food or fluid (except water) should be ingested until the end of the sample period (6 hours after lunch). An indwelling canula will be placed into one of your antecubital veins prior to the test meal. 12ml blood samples will be taken just before your lunch, then at 15, 30, 45, 60, 75, 90, 120, 150, 180, 240, 270, 300 and 360 mins later. You may then eat and drink anything you want. Please note, you must not donate blood for at least 4 months after the last leg of the study.

A diagram of the study is attached. *(A copy of the study schedule shown earlier will be provided to the subjects)*.

**RIGHTS OF THE SUBJECT**

You are asked to take part in this trial voluntarily. You are free to withdraw from the trial at any time and the medical supervisor or principal investigator is free to withdraw you for medical or administrative reasons, or protocol violations. You may be asked your reason for withdrawing, but you are not obliged to give any.
CONFIDENTIALITY
All information which you give or which is collected about you will be treated as highly confidential. None of the documents reporting the trial will identify you by name. If the results are published in medical journals, your privacy will be maintained.

The results obtained in this study may be valuable in the identification and possible prevention of risk factors that may be harmful to the health of shift workers.
I, the undersigned, voluntarily agree to take part in the study SHIFTSIM/NUTR/97.

I have been given a full explanation by the scientific investigators of the nature, purpose and likely duration of the study and what I will be expected to do.

I have been given the opportunity to question the investigators on all aspects of the study, and have understood the advice and information given as a result.

I agree to comply with any instruction given to me during the study and to co-operate fully with all the study staff, informing them immediately of any problems that may have arisen.

All documentation held on a volunteer is in the strictest confidence and complies with the Data Protection Act (1984). I agree that I will not seek to restrict the use to which the results of the study may be put.

I understand that I am free to withdraw from the study at any time without needing to justify my decision and without prejudice.

I confirm that I have read and understood the above and freely consent to participating in this study. I have been given adequate time to consider my participation and agree to comply with the instructions and restrictions of the study.

Information on any aspect of this study can be obtained by contacting Richard Barnes on 01483 259712.

Name of volunteer ...........................................
(BLOCK CAPITALS)

Signature of volunteer ...........................................

Date ...........................................
### SLEEP LOG
Shift work simulation study

<table>
<thead>
<tr>
<th>Subject Name</th>
<th>Date</th>
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<tr>
<th>Time of going to bed</th>
<th>Started trying to sleep at</th>
<th>Estimated time taken to fall asleep (mins)</th>
<th>Estimated number of night awakenings</th>
<th>Estimated total time of awakenings (mins)</th>
<th>Time of waking up</th>
<th>Time of getting out of bed</th>
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<tr>
<td></td>
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<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>How rested do you feel after sleep?</th>
<th>How would you rate your overall sleep quality?</th>
</tr>
</thead>
<tbody>
<tr>
<td>well rested</td>
<td>extremely poor</td>
</tr>
<tr>
<td>not at all rested</td>
<td>extremely good</td>
</tr>
</tbody>
</table>
Appendix III

Melatonin Study Protocol
Protocol Title: Assessment of the ability of exogenous melatonin to facilitate adaptation to a normal routine following night shift in oil rig shift workers at home.

Principal Investigator: Richard Barnes
Address: Chronobiology Laboratory
School of Biological Sciences
University of Surrey
Guildford
Surrey, GU2 5XH
Telephone/Fax no: 01483 259712

Sponsors: Stockgrand Ltd.
School of Biological Sciences
University of Surrey
Guildford
Surrey, GU2 5XH

Shell U.K. ExPro
1, Altens Farm Road
Nigg
Aberdeen, AB9 2HY

Name of Ethics Committee: University of Surrey's Advisory Committee on Ethics (USACE)
Address: c/o Sarah Kitchen, Secretary
Senate House
University of Surrey
Guildford
Surrey, GU2 5XH

RESPONSIBLE PERSONNEL

<table>
<thead>
<tr>
<th>Name</th>
<th>Title Designation</th>
<th>Location</th>
<th>Office Phone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mr. R. Barnes</td>
<td>Principal Investigator, PhD Student.</td>
<td>Chronobiology Laboratory, University of Surrey</td>
<td>01483 259712</td>
</tr>
<tr>
<td>2. Dr. M. J. Forbes</td>
<td>Senior Medical Advisor, Shell ExPro.</td>
<td>Shell U.K. ExPro 1, Altens Farm Road Aberdeen</td>
<td>01224 883031</td>
</tr>
<tr>
<td>6. Prof. J. Arendt</td>
<td>Principal Supervisor, Managing Director, Stockgrand Ltd.</td>
<td>Chronobiology Laboratory, University of Surrey</td>
<td>01483 259701</td>
</tr>
<tr>
<td>7. Dr. S. Deacon</td>
<td>Academic Supervisor.</td>
<td>Chronobiology Laboratory, University of Surrey</td>
<td>01483 300800 ext. 2520</td>
</tr>
<tr>
<td>Title</td>
<td>Assessment of the ability of exogenous melatonin to facilitate adaptation to a normal routine following night shift in oil rig shift workers at home.</td>
<td></td>
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<td>-------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------</td>
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<tr>
<td>Sponsors</td>
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<td>Project Phase</td>
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<tr>
<td>Objectives</td>
<td>To facilitate readaptation of shift workers into a normal routine at home following a fortnight of night shift on oil installations.</td>
<td></td>
<td></td>
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<tr>
<td>Study Design</td>
<td>Control period: 12 day study (last 2 days of night shift and 9 days leave) measuring subjective sleep and mood, activity, and 3 hourly urinary 6-sulphatoxymelatonin and caffeine. Treatment period: Randomised, double-blind, placebo controlled. Two 12-day studies (as above) with treatment of melatonin or placebo for the first 5 days of leave, followed by 2 days wash out on placebo. Same frequency, type and duration measurements as above except urine collection only for the first two days and after the wash out period.</td>
<td></td>
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<tr>
<td>Planned Total Sample Size</td>
<td>20 control room operators/operations technicians.</td>
<td></td>
<td></td>
</tr>
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<td>Subject Selection Criteria</td>
<td>Oil-rig control room operators and operations technicians involved in a rotating 12 hour shift system.</td>
<td></td>
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<tr>
<td>Formulations</td>
<td>Synthetic melatonin in a lactose filler and gelatin capsule.</td>
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<td>Test drug dose</td>
<td>5mg melatonin</td>
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<tr>
<td>Treatment duration</td>
<td>Single dose, 30 minutes before bedtime, for the first 5 days of leave.</td>
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<td>Concurrent controls</td>
<td>Matched placebo.</td>
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<td>Routes of administration</td>
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<tr>
<td>Main Measurement Parameters</td>
<td>Activity via wrist activity meters and urinary 6-sulphatoxymelatonin (melatonin metabolite) and caffeine. Sleep logs, mood assessments and a standard shiftwork index questionnaire.</td>
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<td>Main Parameters of Safety</td>
<td>Consent of Volunteers' G.P. Inclusion/exclusion criteria.</td>
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APPENDIX 4 SLEEP LOG AND MOOD ASSESSMENT SHEET 16
15. BACKGROUND AND RATIONALE

15.1. Background

Shift-work leads to forced desynchronisation of internal rhythms both from the external environment and from each other, with consequent problems of behaviour (e.g. sleep), physiology (e.g. gut function) and performance (e.g. accident rate). Similar disorganisation of daily rhythms is seen in jet-lag, the aged, some blind subjects and in certain pathological situations (e.g. delayed sleep phase insomnia). It has been suggested that rotating shift-workers may develop significant abnormalities of the entero-insular axis in response to abrupt phase shifts. These may be important in the development of diseases such as coronary heart disease, observed in shift workers by Knutsson (1989), and non-insulin dependent diabetes mellitus.

Hence, many problems may arise from undergoing shift-work, both detrimental to the worker’s long term health (e.g. diabetes), short term health (e.g. industrial accident) and general well-being (e.g. fatigue and mood). Since as much as 20% of the population of developed countries are involved in shift-work (e.g. nurses, police), these problems are of considerable importance.

15.2. Rationale

The hormone melatonin plays an important role in the regulation of many circadian rhythms such as body temperature, alertness and sleep. Administration of oral melatonin has been shown to shift the timing of the body clock in healthy sighted adults and to synchronise the sleep/wake rhythms of blind subjects (who receive no light/dark cycle as a daily time cue) to a normal 24 hour environment and improve alertness at the appropriate times (e.g. Deacon & Arendt, 1995; Folkard et al., 1990). In other situations where the local time cues are quickly altered, e.g. in night shift work and time zone travel, it can take many days for the body clock to adapt to the new shift in local time cues with consequent sleep and alertness/performance problems. Treatment with melatonin has been shown to improve both physiological and behavioural adaptation in these cases (e.g. Arendt et al., 1987; Deacon & Arendt, 1996; Folkard et al., 1993). Melatonin also has acute sleepiness inducing effects in healthy individuals, which may be acting through acute thermodregulatory effects (Dawson & Encel, 1993) and may therefore provide a means of maintaining sleep where biological rhythm and/or sleep disturbances occur.

Our previous work (not published) has shown that both the melatonin rhythm and sleep/wake cycle, of oil rig shift workers, are fully adapted to a night active environment at the end of the two-week night shift. Hence, they must go through a period of readaptation on their time off (leave), during which lowered day time alertness and poor night-time sleep lead to reduced quality of life. Correctly timed melatonin administration should not only increase the rate of readaptation but also increase night-time sleep duration and quality.

16. OBJECTIVES OF THE STUDY

- To investigate the circadian status of oil-rig shift-workers returning home from night shift.
To assess the ability of exogenous melatonin administration to increase the rate of re-adaptation into a normal day-active environment.

17. EXPERIMENTAL DESIGN AND METHODS

17.1. Overall design

The randomised, double-blind, placebo controlled study will involve three separate sampling periods, covering 12 days each, allowing each subject exposure to the three different conditions of melatonin, placebo and no treatment. Days -2 and -1 are the last 2 days on night shift; days 0 to 9 are the first 10 days of leave (time off). Six weeks will separate each study period. The subjects will continue with their normal routine.

17.2. Number and source of subjects

Potentially 20 subjects will be recruited from Tern Alpha and Cormorant Alpha oil-rig.

17.3. Centre

The study will be conducted in the volunteers home environment.

17.4. Measurements

- Urine:
  Control study: Urine will be collected sequentially over 24 hour periods every 3 hours (7/8 hours when asleep) for the whole study period. The subjects will measure and record the total volume of each sample and aliquot 2 ml samples for freezing. The subjects are allowed to urinate in between collection periods, but this is collected in the bottles provided and the total for that period is measured.
  Treatment studies: Urine will be collected as in the control study except only for 2 days before the end of night shift (days -2 and -1) and the last 3 days of the study (days 7, 8 and 9).

- Activity: Wrist activity meters will be worn by the subjects at all times during the study periods, apart from when in the shower. The meters are similar in size to a watch and will not cause any restrictions to the wearers.

- Subjective sleep logs and mood assessment: Subjects will fill in subjective estimations of sleep quality, duration, latency and number and duration of awakenings after every period of sleep or nap. Mood will be rated on visual analogue scales (see Appendix 4) every 3 hours when awake.
Questionnaire: Each subject will complete one Standard Shiftwork Index questionnaire (Barton et al, 1990) asking questions on home life, work environment/shift system, personality and nutrition.

17.5. Urine sample analysis

All the samples will be immediately frozen, and then transported back to the Chronobiology Laboratory in the School of Biological Sciences (University of Surrey), at the end of the study, for analysis. Urinary 6-sulphatoxymelatonin (melatonin metabolite) will be measured, by a specific radioimmunoassay technique, to assess circadian status. This metabolite is the best marker of the behaviour of the body clock in field studies, with non-invasive collection.

17.6. Melatonin and placebo administration

The control study will have no melatonin or placebo administration. The treatment studies will have either 5 days of melatonin (5mg) administration (days 0 to 4) followed by 5 days of placebo (days 5 to 9), or 9 days of placebo only (days 0 to 9).

18. SUBJECT SELECTION CRITERIA

18.1. Inclusion Criteria

- Males.
- Aged 18 years or over.
- Healthy individuals free of medication other than minor analgesics.
- Able and willing to give informed written and oral consent.

18.2. Exclusion criteria

- Personal or family history of psychiatric disorder, migraine or epilepsy.
- Unable to provide written consent from a doctor.

19. SCREENING PROCEDURES FOR STUDY ENTRY

19.1. Doctor’s consent

Consent of a doctor is considered to be sufficient in addition to the volunteers informed consent.
19.2. Instructions to Subjects

See Appendix 1

20. WITHDRAWAL OF SUBJECTS FROM STUDY

Subjects have the right to withdraw from the study at any time for any reason without prejudice. The Medical Supervisor and Principle Investigator also has the right to withdraw subjects from the study in the event of concomitant illness, adverse events, protocol violations, administrative reasons or other reasons.

At the time of withdraw, an explanation of why the subject is withdrawing from the study will be determined as completely as possible. However, the subject is not obliged to give a reason for withdrawing from the study.

21. DETAILS ABOUT THE MELATONIN COMPOUND

Melatonin is a natural hormone produced by the pineal gland within the brain. The product used in the study is synthetic but identical to the natural compound in structure. It is only available in the UK on prescription. It is provided by Penn Pharmaceuticals Ltd., Tredegar, Wales, who are licensed to sell this medication on a named patient basis. The Department of Health do not require notification of trials using oral doses up to 10mg in healthy volunteers. In previous trials of oral melatonin, the dose used was 5mg (exceptionally 10mg) daily per os for 4-7 days. This dose has been used successfully in more than 474 "jet lag" subjects during the last 10 years in Professor Arendt's work and in many other subjects in others' work, both for jet lag, delayed sleep phase insomnia, sleep disturbance in shift workers, in the blind and in the elderly (e.g. Arendt et al, 1987; Arendt and Aldhous, 1988; Jan et al, 1994; Wright et al, 1986; Zaidan et al, 1994; Garfinkel et al, 1995; Deacon & Arendt, 1996). Professor Arendt and Dr Deacon have previously been granted ethical approval from the University of Surrey's Advisory Committee on Ethics for many melatonin administration studies. The only reported side effects to date using melatonin to alleviate jet lag (in house study) are reported in the Table (7.1). It is also being assessed for immunostimulatory activity and as a free radical scavenger. In very much larger doses (80-300mg daily) in combination with a progestagen it is under assessment as a female oral contraceptive. The doses used in this study will be 5mg oral doses.
Table 7.1 Percentage side-effects reported more than once after taking melatonin (5mg) to alleviate jet lag (Arendt, University of Surrey).

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>Placebo (n=112)</th>
<th>Melatonin (n=474)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleepiness</td>
<td>1.78</td>
<td>8.3</td>
</tr>
<tr>
<td>Headache</td>
<td>2.7</td>
<td>1.65</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>1.4</td>
</tr>
</tbody>
</table>

22. SHELL AND HSE APPROVAL
This study has been approved by Shell (UK) Exploration and Production medical department and the Health and Safety Executive (See Appendix 5).
23. REFERENCES

APPENDIX 1
SUBJECT INFORMATION SHEET

STUDY: SHIFTWORK/MT/97

You are invited to take part in a study designed to evaluate the ability of melatonin (N-acetyl-5-methoxytryptamine) to facilitate adaptation to a normal routine following night shift.

Melatonin (N-acetyl-5-methoxytryptamine) is a natural hormone produced by the pineal gland normally at night. It serves to help coordinate biological timing systems, for example that of sleep. In large amounts (300 milligrams daily) it can suppress reproductive function in humans. It may have some anti-tumour activity. It has been administered in humans since the 1960's in doses of up to 1 gram daily and has been used extensively at doses of 5 milligrams to investigate its ability to alleviate jet lag and improve sleep in night shift workers, blind people and patients with delayed sleep phase insomnia. Daily doses of up to 5 milligrams melatonin for periods of up to one month have been used extensively in Professor Arendt's work over the past ten years. The table below shows the very low incidence of side-effects from taking melatonin (5mg) or placebo (dummy) in field studies on the alleviation of jet lag (at November 1994).

Percentage side-effects reported more than once after taking melatonin (5mg) to alleviate jet lag.

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>Placebo (112 volunteers)</th>
<th>Melatonin (474 volunteers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleepiness</td>
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<td>0.8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>1.4</td>
</tr>
</tbody>
</table>

YOU MUST INFORM US OF ANY ADVERSE EVENTS THAT OCCUR DURING OR IMMEDIATELY AFTER YOUR PARTICIPATION IN THE STUDY.
PLEASE NOTE THAT MELATONIN CAN INDUCE DROWSINESS AND LOWERED ALERTNESS IN SENSITIVE INDIVIDUALS. YOU ARE ADVISED NOT TO DRIVE FOR 4-5 HOURS AFTER MELATONIN INGESTION.

Shift-work results in a mismatch between internal biological rhythms and the external environmental and behavioural time cues (such as the light-dark cycle, meal times, imposed sleep-wake cycle etc.). A similar occurrence is experienced in the jet lag state. Your body can normally adjust to such changes in the environment, but this process usually takes several days for full adaptation. The resulting desynchronisation can result in fatigue, sleeplessness, reduced performance, lowered mood, indigestion etc.

The aim is to help alleviate some or all of these problems allowing greater comfort and well-being in your leisure and sleep. This treatment phase will assess the ability of the hormone melatonin to increase the rate of readaptation to a normal day pattern following night shift.
This trial has been reviewed by an independent Ethics Committee which had no objections to its taking place.

**PROcedures:**

**Pre-Study**

Your date of birth, sex, height, weight and race will be recorded, all of which will remain confidential.

You will be given the opportunity to familiarise yourself with the equipment you will be using in the trial.

**During the Study**

**Days -2 and -1 (Last Two Days on Night Shift)**

Urine collection: Urine samples are required every 3 hours. Plastic containers will be provided for urine collection. A urine sample must be given at the end of each 3 hour collection period and the time noted. You may go to the toilet within each period, but any additional urine must also be collected in the same plastic container for that period. Samples are not required every 3 hours throughout your sleep period, but a sample must be given when you get up and the time noted. Any urine collected during the sleep period must be stored in the containers provided and mixed with the sample obtained upon rising. At the end of each period the volume of the urine collected must be measured and recorded, and a small sample placed in a vial provided. The small samples must then be frozen until transport to the University of Surrey, where they will be analysed for a specific marker of biological rhythms.

Mood assessment: Your mood must be recorded on visual analogue scales every 3 hours during your time awake. These are simple linear scales which only take approximately 1 minute to complete. You are asked how you currently feel about various things. For example, you will be asked to rate your alertness as follows:

How alert do you feel at the moment?

<table>
<thead>
<tr>
<th>Very drowsy</th>
<th>Very alert</th>
</tr>
</thead>
</table>

The middle of the line represents a feeling halfway between the two extremes. Position a cross at any point along the line: the further to the right the more alert you feel, the further to the left the more drowsy you feel.

Sleep log: You must fill out a sleep log after every sleep period which asks for bed and wake-up times, sleep quality, and number of awakenings.
**DAYS 1 (RETURN HOME). 2, 3, 4, 5, 6**

Mood assessment: Every 3 hours during your time awake.

Melatonin/placebo administration (days 1 to 4 only): A pill to be taken 30 minutes before going to bed. Pills must be taken in order of day as indicated. You will not be told whether you are taking melatonin or placebo until after the study.

Sleep log: After every sleep or nap period.

NO URINE COLLECTION REQUIRED.

**DAYS 7, 8, 10, 11, 12**

Mood assessment: Every 3 hours during your time awake, including a sample at bedtime and another upon waking.

Urine collection: As above, every 3 hours when awake, including a sample at bedtime and another upon waking.

Melatonin/placebo administration: A pill to be taken up to 30 minutes before going to bed (time must be noted). Pills must be taken in order of day as indicated.

Sleep log: After every sleep or nap period.

**DAY 10**

Mood assessment: Upon waking only.

Urine collection: Last sample upon waking.

Sleep log: Upon waking.

Samples are to be returned to the University of Surrey securely via a delivery service agreed with the principal investigator. Postage will be paid.

**RIGHTS OF THE SUBJECT**

You are asked to take part in this trial voluntarily. You are free to withdraw from the trial at any time and the medical supervisor or principal investigator is free to withdraw you for medical or administrative reasons, or protocol violations.

**CONFIDENTIALITY**
All information which you give or which is collected about you will be treated as highly confidential. None of the documents reporting the trial will identify you by name. If the results are published in medical journals, your privacy will be maintained.

The results obtained in this study may be valuable in the development of treatments of potential benefit to yourself and others.
APPENDIX 2

VOLUNTEERS CONSENT FORM

I, the undersigned, voluntarily agree to take part in the study SHIFTWORK/MT/97.

I have been given a full explanation by the scientific investigators of the nature, purpose and likely duration of the study and what I will be expected to do.

I have been given the opportunity to question the investigators on all aspects of the study, and have understood the advice and information given as a result.

I agree to comply with any instruction given to me during the study and to co-operate fully with all the study staff, informing them immediately of any problems that may have arisen.

All documentation held on a volunteer is in the strictest confidence and complies with the Data Protection Act (1984). I agree that I will not seek to restrict the use to which the results of the study may be put.

I understand that I am free to withdraw from the study at any time without needing to justify my decision and without prejudice.

I confirm that I have read and understood the above and freely consent to participating in this study. I have been given adequate time to consider my participation and agree to comply with the instructions and restrictions of the study.

Information on any aspect of this study can be obtained by contacting Richard Barnes on 01483 259712.

Name of volunteer ...........................................
(BLOCK CAPITALS)

Signature of volunteer ...........................................

Date .............................................
APPENDIX 3
LETTER TO G.P.

SCHOOL OF BIOLOGICAL SCIENCES, University of Surrey, Guildford,
Surrey, GU2 5XH, U.K.
Telephone 01483 300800 extension:9701 Direct Line 01483 259701
Fax: 01483 259712

To Dr.

A patient of yours M.

Address

has volunteered to take part in a trial designed to evaluate the phase shifting ability of melatonin (N-acetyl-5-methoxytryptamine) in readapting to a normal routine following night shift. We would like you to inform us if you are unhappy with M........................................ taking part in this study.

Melatonin is a natural hormone produced by the pineal gland. The product used in the study is synthetic but identical to the natural compound in structure. It is provided by Penn Pharmaceuticals who are licensed to sell this unregistered medication by the Department of Health. The Department of Health does not consider that trials in healthy volunteers need to be notified. In previous trials of oral melatonin, the dose used was 5mg (exceptionally 10mg) daily per os for 4-7 days. This dose has been used successfully for the treatment of jet lag in more than 484 subjects during the last 10 years in my own work and in many other subjects in others' work, both for jet lag, delayed sleep phase insomnia, sleep disturbance in shift workers, in the blind and in the elderly. The only reported side effects to date are sleepiness (8.3%), headache (2.7%), nausea (0.9%) feeling fuzzy/giddy (1.4%). Placebo studies in 112 subjects have shown the following: sleepiness (1.78%), headache (1.65%), nausea (0.8%) and fuzzy/giddy (0%). It is also being assessed for immunostimulatory activity and as a free radical scavenger. In very much larger doses (80-300mg daily) in combination with a progestagen it is under assessment as a female oral contraceptive. In the present trial, melatonin will be administered in 5mg doses.

Subjects sign an informed consent form and may only take part if they are over 18 years old, healthy, free of medication other than minor analgesics and with no personal or family history of psychiatric disorder.

Should you require any further information, please contact Professor Josephine Arendt on 01483 259701 or Richard Barnes on 01483 259712.
Please inform us as soon as possible if you are unhappy with M............................................ taking part in this study, and return to me in the prepaid, preaddressed envelope.

Yours sincerely,

Josephine Arendt, PhD, FRCPaht
Professor of Endocrinology
APPENDIX 4

SLEEP LOG
Shift Work Circadian Rhythm Studies

| Subject Name : | Date : | Time : |

| Time of going to bed : | Started trying to sleep at : |

| Estimated time taken to fall asleep (mins) : | Estimated number of night awakenings: |

| Estimated total time of awakenings (mins) : | Time of waking up : |

| Time of getting out of bed : |

| How rested do you feel after sleep? | How would you rate your overall sleep quality? |

| well rested | extremely good | not at all rested | extremely poor |

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# ALERTNESS ASSESSMENT
Cormorant Alpha Circadian Rhythm Studies

<table>
<thead>
<tr>
<th>Subject Name: __________________________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date: _______  Time: _______</td>
</tr>
<tr>
<td>Very drowsy</td>
</tr>
<tr>
<td>Date: _______  Time: _______</td>
</tr>
<tr>
<td>Very drowsy</td>
</tr>
<tr>
<td>Date: _______  Time: _______</td>
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<tr>
<td>Very drowsy</td>
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<td>Date: _______  Time: _______</td>
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<tr>
<td>Very drowsy</td>
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<tr>
<td>Date: _______  Time: _______</td>
</tr>
<tr>
<td>Very drowsy</td>
</tr>
<tr>
<td>Date: _______  Time: _______</td>
</tr>
<tr>
<td>Very drowsy</td>
</tr>
</tbody>
</table>
Appendix IV

Nutrition Field Study Protocol
PROTOCOL FOR SUBMISSION TO USACE

Protocol Title: Post-prandial hormone and metabolic response of oil rig shiftworkers to a test meal on night shift.

Principal Investigator: Richard Barnes
Address: Chronobiology Laboratory
School of Biological Sciences
University of Surrey
Guildford
Surrey, GU2 5XH
Telephone/Fax no: 01483 259712

Sponsors: Stockgrand Ltd.
School of Biological Sciences
University of Surrey
Guildford
Surrey, GU2 5XH

Name of Ethics Committee: University of Surrey’s Advisory Committee on Ethics (USACE)
Address: c/o Sarah Bryan, Secretary
Senate House
University of Surrey
Guildford
Surrey, GU2 5XH

RESPONSIBLE PERSONNEL

<table>
<thead>
<tr>
<th>Name</th>
<th>Title Designation</th>
<th>Location</th>
<th>Office Phone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mr. R. Barnes</td>
<td>Principal Investigator. PhD Student.</td>
<td>Chronobiology Laboratory, University of Surrey</td>
<td>01483 259712</td>
</tr>
<tr>
<td>2. Dr. M. J. Forbes</td>
<td>Senior Medical Advisor, Shell ExPro.</td>
<td>Shell U.K. ExPro 1, Alten Farm Road Aberdeen</td>
<td>01224 883031</td>
</tr>
<tr>
<td>3. Dr. B. Griffin</td>
<td>Collaborative nutrition investigator.</td>
<td>Nutrition Research Group, University of Surrey.</td>
<td>01483 300800 ext. 2509</td>
</tr>
<tr>
<td>4. Dr. S. M. Hampton</td>
<td>Collaborative endocrinology investigator.</td>
<td>Endocrinology and Metabolism Group, University of Surrey.</td>
<td>01483 259732</td>
</tr>
<tr>
<td>5. Prof. J. Arendt</td>
<td>Principal Supervisor. Managing Director, Stockgrand Ltd.</td>
<td>Chronobiology Laboratory, University of Surrey</td>
<td>01483 300800 ext. 2504</td>
</tr>
<tr>
<td>6. Dr. S. Deacon</td>
<td>Academic Supervisor.</td>
<td>Chronobiology Laboratory, University of Surrey</td>
<td>01483 300800 ext. 2520</td>
</tr>
</tbody>
</table>
**Title** | Post-prandial hormone and metabolic response of oil rig shiftworkers to a test meal on night shift.
---|---
**Sponsors** | Stockgrand Ltd.
**Project Phase** | Nutrition assessment.
**Objectives** | To determine the post-prandial hormone and metabolic response to a fixed, test meal at various intervals throughout a two-week night shift. To identify potential risk factors associated with coronary heart disease, atherosclerosis and diabetes.
**Study Design** | Control period: Two-week day shift. Meal studies on days 2, 8 and 14. Test period: Two-week night shift. Meal studies on days 2, 8 and 14.
**Planned Total Sample Size** | 20 control room operators/operations technicians.
**Subject Selection Criteria** | Oil-rig control room operators and operations technicians involved in a rotating 12 hour shift system.
**Test meal** | High carbohydrate pre-meal: Corn flakes (50g) with milk (200ml), decaffeinated coffee/tea and orange juice (200ml). Test meal: Baked potato, baked beans (½ tin), cheese (2oz) and orange juice (200ml).
**Controls** | The same individuals repeat the study on day shift.
**Main Measurement Parameters** | Circadian measurements: Activity (via wrist activity meters), urinary 6-sulphatoxymelatonin (melatonin metabolite), sleep logs and mood assessments. Nutritional measurements: Plasma insulin, glucose, c-peptide, GIP, TAG, NEFA. Plasma LDL (low density lipoproteins) subclasses. Additional measurements: Urinary caffeine and a standard shiftwork index questionnaire.
**Main Parameters of Safety** | Consent of Volunteers' G.P. Inclusion/exclusion criteria.
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   1.2. Rationale

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   3.3. Centre
   3.4. Measurements
   3.5. Sample analysis
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   4.1. Inclusion Criteria
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5. SCREENING PROCEDURES FOR STUDY ENTRY
   5.1. Doctor's consent
   5.2. Instructions to Subjects

6. WITHDRAWAL OF SUBJECTS FROM STUDY

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LETTER OF MEDICAL COVER  

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1. BACKGROUND AND RATIONALE

1.1. Background

Shift-work leads to forced desynchronisation of internal rhythms both from the external environment and from each other, with consequent problems of behaviour (e.g. sleep), physiology (e.g. gut function) and performance (e.g. accident rate). Similar disorganisation of daily rhythms is seen in jet-lag, the aged, some blind subjects and in certain pathological situations (e.g. delayed sleep phase insomnia). It has been suggested that rotating shift-workers may develop significant abnormalities of the entero-insular axis in response to abrupt phase shifts. These may be important in the development of diseases such as coronary heart disease (CHD), observed in shift workers by Knutsson (1989), and non-insulin dependent diabetes mellitus (NIDDM). Hence, many problems may arise from undergoing shift-work, both detrimental to the worker’s long term health (e.g. diabetes), short term health (e.g. industrial accident) and general well-being (e.g. fatigue and mood). Since as much as 20% of the population of developed countries are involved in shift-work (e.g. nurses, police) these problems are of considerable importance.

1.2. Rationale

The mechanism by which shiftwork leads to CHD and possibly NIDDM is still unclear, but there is increasing evidence that it is an inappropriate metabolic response to meals at times out of phase with the body clock that may promote risk factors. If this proves to be correct then not only will problems arise at the start of a night shift, but also at the end of night shift when changing back to a normal routine (or day shift) if full adaption has occurred.

Glucose tolerance has been shown to decrease throughout the day and into the night in normal individuals (Service et al, 1983), and it is now clear that glucose and insulin responses are modulated by circadian rhythmicity (Van Cauter et al, 1992). Other factors have also been seen to exhibit diurnal variation, such as gut hormones (e.g. glucose-dependent insulinotropic polypeptide (GIP)) and non-esterified fatty acids (NEFAs). A recent study by our group has shown significantly altered pancreatic B-cell responses and postprandial glucose and lipid metabolism in simulated shiftwork (Hampton et al, 1996). The observed reduced clearance of triacylglycerol (TAG), during the simulated shiftwork, may be especially important in the development of CHD in relation to its influence on low density lipoprotein (LDL) profiles.

A predominance of small, dense LDL (LDL-III density 1.040-1.063g/ml) in plasma has been associated with a 4 to 6-fold increase in coronary heart disease risk (Griffin et al, 1994) and has been implicated in atherosclerosis through its increased susceptibility to oxidative modification (Griffin et al, 1993) and selective binding to arterial proteoglycans (Anber et al, 1996). Small, dense LDL is a well established feature of an atherogenic lipoprotein phenotype, the dyslipidaemia of insulin resistance present in NIDDM, and as such has been strongly linked with the phenomenon of triglyceride intolerance, enhanced post-prandial lipaemia and reduced levels of putatively protective HDL.

This study will examine the post-prandial hormone and metabolic responses to a test meal of oil rig workers on day shift and night shift under field conditions. The responses will be measured on three separate occasions over the shifts and related to
the phase position of the biological clock (as assessed by measurement of the melatonin metabolite 6-sulphatoxymelatonin in urine). Our previous work (not yet published) has shown that both the melatonin rhythm and sleep/wake cycle, of oil rig shift workers, are fully adapted to a night active environment at the end of a two-week night shift. Levels of insulin resistance, lipid metabolism and lipoprotein phenotype will be monitored to identify potential risk factors associated with CHD, atherosclerosis and NIDDM.

2. OBJECTIVES OF THE STUDY

- To determine the post-prandial hormone and metabolic response to a fixed, test meal at various intervals throughout a two-week night shift.
- To identify potential risk factors associated with coronary heart disease, atherosclerosis and diabetes.

3. EXPERIMENTAL DESIGN AND METHODS

3.1. Overall design

The study will involve a test period and a control period of two-weeks duration each. The control period will cover the day shift and the test period will cover the night shift of the same individuals. Both are identical except that the timing of the test meal and blood sampling will be dependent on the shift worked. Study day 1 is the first day on the rig. Study day 2 is the first full day of day shift or the first full night of night shift. Study day 14 is the last full day of day shift or the last full night of night shift. The meal studies will be conducted on days 2, 8 and 14. Circadian measurements will be conducted on days 1, 2, 3, 7, 8, 9, 12, 13 and 14. The study design is summarised in table 1.

Table 1: Study design

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<th>6</th>
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</thead>
<tbody>
<tr>
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</tr>
</tbody>
</table>

3.2. Number and source of subjects

Potentially 10 subjects will be recruited from Tern Alpha and Cormorant Alpha oil installations.
3.3. Centre

The study will be conducted on the Tern Alpha and Cormorant Alpha oil installations.

3.4. Measurements

- Urine: Urine will be collected sequentially over 24 hour periods every 3 hours (7/8 hours when asleep) for study days 1, 2, 3, 7, 8, 9, 12, 13 and 14. The investigator will measure and record the total volume of each sample and aliquot 2 ml samples for freezing. The subjects are allowed to urinate in between collection periods, but this is collected in the bottles provided and the total for that period is measured.

- Activity: Wrist activity meters will be worn by the subjects at all times during the study periods, apart from when in the shower. The meters are similar in size to a watch and will not cause any restrictions to the wearers.

- Subjective sleep logs and mood assessment (see Appendix 4): Subjects will fill in subjective estimations of sleep quality, duration, latency and number and duration of awakenings after every period of sleep or nap. Mood will be rated on visual analogue scales every 3 hours when awake on days 1, 2, 3, 7, 8, 9, 12, 13 and 14.

- Questionnaire: Each subject will complete one Standard Shiftwork Index questionnaire (Barton et al, 1990) asking questions on home life, work environment/shift system, personality and nutrition.

- Blood: Three samples (25ml) taken by venepuncture on each test meal day at the following times: 0 mins (immediately before test meal), 30 mins and 240 minutes. The blood will be taken by a qualified paramedic who maintains a constant presence on the rig.

3.5. Sample analysis

3.5.1. Urine analysis

All the samples will be immediately frozen, and then transported back to the Chronobiology Laboratory in the School of Biological Sciences (University of Surrey), at the end of the study, for analysis. Urinary 6-sulphatoxymelatonin (melatonin metabolite) will be measured, by a specific radioimmunoassay technique, to assess circadian status. This metabolite is the best marker of the behaviour of the body clock in field studies, with non-invasive collection. Urinary caffeine will be measured by an ELISA technique.
3.5.2. Blood analysis

All the samples will be immediately centrifuged and the plasma extracted and frozen for transportation to the University of Surrey. Plasma glucose, NEFAs and TAG will be measured by standard automated enzymatic spectrophotometry. Insulin and GIP will be measured by radioimmunoassay. The proportions and plasma concentrations of the three principal LDL subclasses (LDL-I, II and III) are calculated from LDL subclass profiles generated by spectrophotometric monitoring (Griffin et al. 1990).

3.6. Test meal

- Low fat pre-meal (breakfast): Corn flakes (50g), 1 cup of decaffeinated coffee/tea, orange juice (200ml), milk (200ml) and sugar (25g) for cereal and hot beverage.
Test meal (lunch): Large baked potato, baked beans (½ tin), cheese (2oz) and orange juice (200ml).

4. SUBJECT SELECTION CRITERIA

4.1. Inclusion Criteria

- Males.
- Aged 18 years or over.
- Healthy individuals free of medication other than minor analgesics.
- Able and willing to give informed written and oral consent.

4.2. Exclusion criteria

- Unable to provide written consent from a doctor.

5. SCREENING PROCEDURES FOR STUDY ENTRY

5.1. Doctor’s consent

Consent of a doctor is considered to be sufficient in addition to the volunteers informed consent.

5.2. Instructions to Subjects

See Appendix 1

6. WITHDRAWAL OF SUBJECTS FROM STUDY
Subjects have the right to withdraw from the study at any time for any reason without prejudice. The Medical Supervisor and Principle Investigator also has the right to withdraw subjects from the study in the event of concomitant illness, adverse events, protocol violations, administrative reasons or other reasons.

At the time of withdraw, an explanation of why the subject is withdrawing from the study will be determined as completely as possible. However, the subject is not obliged to give a reason for withdrawing from the study.
7. REFERENCES


APPENDIX 1

SUBJECT INFORMATION SHEET

STUDY: SHIFTWORK/NUTR/97

This trial has been reviewed by an independent Ethics Committee which had no objections to its taking place. *(To be added once approved).* The study will cover one night shift and one day shift.

STUDY OBJECTIVES

There is now increasing evidence that the human body may have difficulty handling food ingested at irregular times to what would be considered normal. It has been suggested that the conflict between internal biological rhythms of hormones, responsible for food digestion, and the external environment may result in the development of abnormalities. Considering the regiment of shiftworkers, this would not only be a problem when starting night shift, but also when returning home on leave. Therefore this study aims to examine the body’s response to a meal on night shift and day shift to determine if abnormalities are present. Future studies will then attempt to reduce the development of any resulting risk factors by increasing the rate of adaptation into and out of night shift.

PROCEDURES:

PRE-STUDY

Your date of birth, sex, height, weight and race will be recorded, all of which will remain confidential.

You will be given the opportunity to familiarise yourself with the equipment you will be using in the trial.

You will be asked to sign a consent form for the study and blood donation.

DURING THE STUDY

DAY 1 (FIRST DAY ON THE RIG)

Activity monitoring: Your general activity and rest will be measured by an activity meter worn on the wrist (except when washing/showering). This device is very similar to a watch, and should cause no undue restrictions.

Urine collection: Urine samples are required every 3 hours. Plastic containers will be provided for urine collection. *A urine sample must be given at the end of each 3 hour collection period and the time noted.* You may go to the toilet within each period, but any additional urine must also be collected in the same plastic container for that period. Samples are not required every 3 hours throughout your sleep period, but a sample must be given when you get up and the time noted. *Any urine collected during the sleep period must be stored in the containers provided and mixed with*
the sample obtained upon rising. At the end of each period the volume of the urine collected will be measured and recorded by the investigator, and a small sample placed in a vial provided. The small samples will be frozen until transport to the University of Surrey, where they will be analysed for a specific marker of biological rhythms.

Mood assessment: Your mood must be recorded on visual analogue scales every 3 hours during your time awake. These are simple linear scales which only take approximately 1 minute to complete. You are asked how you currently feel about various things. For example, you will be asked to rate your alertness as follows:

<table>
<thead>
<tr>
<th>Very drowsy</th>
<th>Very alert</th>
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<tbody>
<tr>
<td></td>
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</table>

How alert do you feel at the moment?

The middle of the line represents a feeling halfway between the two extremes. Position a cross at any point along the line: the further to the right the more alert you feel, the further to the left the more drowsy you feel.

Sleep log: You must fill out a sleep log after every sleep period which asks for bed and wake-up times, sleep quality, and number of awakenings.

**DAYS 2 (FIRST NIGHT OF NIGHT SHIFT OR FIRST FULL DAY OF DAY SHIFT)**

Urine collection: As Day 1.

Activity monitoring: Continuous (except during washing).

Mood assessment: Every 3 hours during your time awake.

Sleep log: After every sleep or nap period.

Blood collection: You will be given a substantial set meal at breakfast and lunch. No other food or fluid (except water) should be ingested until the end of the sample period (4 hours after lunch). A 25ml blood sample will be taken just before your lunch, then 30 mins and 4 hours later. You may then eat and drink anything you want.

**DAY 3**

Urine collection: As Day 1.

Activity monitoring: Continuous (except during washing).

Mood assessment: Every 3 hours during your time awake.

Sleep log: After every sleep or nap period.

**DAYS 4, 5 AND 6**
Activity monitoring: Continuous (except during washing)
Sleep log: After every sleep or nap period.

**DAY 7**
Urine collection: As Day 1.
Activity monitoring: Continuous (except during washing).
Mood assessment: Every 3 hours during your time awake.
Sleep log: After every sleep or nap period.

**DAY 8**
Urine collection: As Day 1.
Activity monitoring: Continuous (except during washing).
Mood assessment: Every 3 hours during your time awake.
Sleep log: After every sleep or nap period.
Blood collection: As Day 1.

**DAY 9**
Urine collection: As Day 1.
Activity monitoring: Continuous (except during washing).
Mood assessment: Every 3 hours during your time awake.
Sleep log: After every sleep or nap period.

**DAYS 10 AND 11**
Activity monitoring: Continuous (except during washing)
Sleep log: After every sleep or nap period.

**DAYS 12 AND 13**
Urine collection: As Day 1.
Activity monitoring: Continuous (except during washing).
Mood assessment: Every 3 hours during your time awake.

Sleep log: After every sleep or nap period.

**DAY 14 (LAST NIGHT OF NIGHT SHIFT OR LAST FULL DAY OF DAY SHIFT)**

Urine collection: As Day 1.

Activity monitoring: Continuous (except during washing).

Mood assessment: Every 3 hours during your time awake.

Sleep log: After every sleep or nap period.

Blood collection: As Day 1.

**STUDY SUMMARY**

<table>
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<th>Day</th>
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**RIGHTS OF THE SUBJECT**

You are asked to take part in this trial voluntarily. You are free to withdraw from the trial at any time and the medical supervisor or principal investigator is free to withdraw you for medical or administrative reasons, or protocol violations.

**CONFIDENTIALITY**

All information which you give or which is collected about you will be treated as highly confidential. None of the documents reporting the trial will identify you by name. If the results are published in medical journals, your privacy will be maintained.

The results obtained in this study may be valuable in the identification and possible prevention of risk factors that may be harmful to your health.
APPENDIX 2

VOLUNTEERS CONSENT FORM

I, the undersigned, voluntarily agree to take part in the study SHIFTWORK/NUTR/97.

I have been given a full explanation by the scientific investigators of the nature, purpose and likely duration of the study and what I will be expected to do.

I have been given the opportunity to question the investigators on all aspects of the study, and have understood the advice and information given as a result.

I agree to comply with any instruction given to me during the study and to co-operate fully with all the study staff, informing them immediately of any problems that may have arisen.

All documentation held on a volunteer is in the strictest confidence and complies with the Data Protection Act (1984). I agree that I will not seek to restrict the use to which the results of the study may be put.

I understand that I am free to withdraw from the study at any time without needing to justify my decision and without prejudice.

I confirm that I have read and understood the above and freely consent to participating in this study. I have been given adequate time to consider my participation and agree to comply with the instructions and restrictions of the study.

Information on any aspect of this study can be obtained by contacting Richard Barnes on 01483 259712.

Name of volunteer ........................................ (BLOCK CAPITALS)

Signature of volunteer ........................................

Date ........................................
APPENDIX 3

SLEEP LOG
Shift Work Circadian Rhythm Studies

Subject Name: ____________________
Date: __________  Time: _________

<table>
<thead>
<tr>
<th>Time of going to bed:</th>
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<tbody>
<tr>
<td>Started trying to sleep at:</td>
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<tr>
<td>Estimated time taken to fall asleep (mins):</td>
<td></td>
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<tr>
<td>Estimated number of night awakenings:</td>
<td></td>
</tr>
<tr>
<td>Estimated total time of awakenings (mins):</td>
<td></td>
</tr>
<tr>
<td>Time of waking up:</td>
<td></td>
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<tr>
<td>Time of getting out of bed:</td>
<td></td>
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</tbody>
</table>

How rested do you feel after sleep?
- well rested | ____________ | all rested

How would you rate your overall sleep quality?
- extremely good | ____________ | extremely poor
MOOD AND ALERTNESS ASSESSMENT
Tern Alpha Circadian Rhythm Studies

Subject Name: ____________________
Date: _______ Time: _______

How do you rate your overall mood at the moment?

Very sad ——————————— Very happy

How calm do you feel at the moment?

Very anxious ———————— Very calm

How energetic do you feel at the moment?

Very lethargic ———— Very energetic

How alert do you feel at the moment?

Very drowsy ———— Very alert
Publications and Presentations
Publications


Presentations


