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THE EFFECTS AND CONSEQUENCES OF INTERACTIONS BETWEEN CIRCADIAN RHYTHMS AND SHIFT WORK

By

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<u>DECLARATION OF OWNERSHIP</u>

This submission is the result of my own work. All help and advice, other than that received from tutors, has been acknowledged and primary and secondary sources of information have been properly attributed. Should this statement prove to be untrue, I recognise the right and duty of the Board of Examiners to recommend what action should be taken in line with the university's regulations on assessment contained in the handbook.

Signed:…………………………………………………. Date:………………….

Preface

I would like to thank my dissertation tutor Dr Shiva Sivasubramaniam for his advice and encouragement in the writing of this dissertation. I would also like to thank the staff in the occupational health centre at the Queens Medical Centre for their advice and help, and the pharmacy department for allowing me to use their resources.

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(5) TREATMENT AND ADAPTION STRATEGIES

Commonly Used Abbreviations

BMI	Body Mass Index

BP	Blood Pressure
CHD	Coronary Heart Disease
COX	Cyclo-oxygenase
EC	European Community
ECG	Electrocardiogram
GABA	Gamma-Aminobutyric Acid
GPCR	G-Protein Coupled Receptor
HDL	High Density Lipoprotein
HR	Heart Rate
HRV	Heart Rate Variability
LFS	Labour Force Survey
MI	Myocardial Infarction
MT	Melatonin
NHS	National Health Service
PCR	Polymerase Chain Reaction
PVC	Premature Ventricular Complexes
SCN	Suprachiasmatic Nucleus
mRNA	messenger Ribonucleic Acid
SAD	Seasonal Affective Disorder
UK	United Kingdom
USA	United States of America

INTRODUCTION

The interaction between shift work and biological rhythms is a popular topic of research, and related papers can be found in a diverse range of journals (see appendix 1). As would be expected with such a range of disciplines, the angle or 'take' on the various components that are studied are very much dependent on the interest of the group that undertakes the work. It is of particular interest to those who are involved in occupational health (Harrington, 2001) and also those who are concerned with endocrine disturbances (Morgan *et al*., 1998).

Shift work is an increasingly common phenomenon, with an increasing number of individuals expected to work out side of the traditional hours of work (Rajaratnam & Arendt, 2001).

This dissertation will focus mainly on individuals that work in the healthcare setting, although the principles also apply to a wide variety of other shift workers. All workers and employers are required under health and safety legislation to minimise risk and harm to both themselves and to those around them. For doctors and nurses, this is reinforced by statutory requirements set out by the governing bodies of each profession. It is therefore important that they (the employees) and their employers understand the implications that inappropriate shift patterns may have on their performance (Lamond & Dawson, 1999), the incidence of injuries (Smith *et al*., 1994), accidents (Mitler, 1988), physiological and psychological damage (Knutsson, 2003); this has both legal and ethical implications. Certainly within the NHS there is a move towards 'evidence based practice' which means that all policies that are to be implemented need to be based on some form of evidence that they are indeed the best course of action.

In the first chapter the incidence and types of shift work are introduced and reviewed, together with the methods used to study them. In the second chapter biological rhythms are introduced, and the way in which they interact with physiological function is discussed. In the third chapter, the maintenance of circadian rhythms is critically evaluated, including the latest research using modern biochemical techniques. The way in which circadian rhythms are entrained is also discussed.

In the fourth chapter, the consequences of circadian disruption are evaluated, in relation to physiological function, or dysfunction.

In the fifth and final chapter the increasing number of treatments and adaptation strategies are critically evaluated to determine what practices could be adopted by both employees and their employers to minimise disruption to shift workers (Horowitz & Tanigawa, 2002).

CHAPTER ONE

INTRODUCTION TO SHIFT WORK

General Employment and Shift Work

The way in which people work is changing to such an extent that the 'Monday to Friday – nine till five' model is no longer standard for a large proportion of the workforce. As patterns of work have changed over the past few decades shift work has become an increasingly common phenomenon (McOrmond, 2004). For example, in spring 2002 the labour force survey (LFS) suggested that approximately 1,769,000 women (16% of total women) and 2,645,000 men (22% of total men) in the UK were employed to either work shifts occasionally or most of the time. In particular, shift work has become increasingly common amongst young working people (16-19) having doubled in the past decade, from one in ten in 1992, to one in five in 2002.

Shift working is essential in a number of extremely important jobs. Nuclear power stations need to be manned 24 hours, as do air traffic control rooms. Hospital patients require 24 hour care and attention. In addition to these 'essential' roles, the public demands that supermarkets are fully stocked in the morning, and that orders are processed and dispatched within tight time schedules.

Different Types of Shift Work: Definitions

There are a number of different shifts that are worked in a variety of work places. The LFS (2002) provides the following definitions:

Three Shift working

Three shift working is when the 24 hours are divided into three shifts – morning (early), afternoon (late) and nights. The day time shifts are typically eight hours in length whilst the night shift is twelve hours.

Continental Shifts

Continental shift working is a continuous three shift system that rapidly rotates between the three types of shift.

Two shift system

This system involves the employee working twelve hour 'double or long day' shifts, commonly 07:00-19:00.

Within the NHS there is a mixture of two and three shift systems operating. Shift patterns have had to be revised in recent years in order to comply with EC working directives.

Different Patterns of Shift Work

This describes the way in which shifts are rotated or alternated between.
Some people for instance may only do one type of shift, for example, permanent nights. Others may do a mixture of different shifts, with varying breaks between

each. Shift patterns may be ‘forward’ rotating or ‘backward’ rotating. The rate at which the shifts are rotated can also vary.

Forward Rotating Shifts

Forward rotating shifts rotate in the direction:

Mornings → Evenings → Nights → Mornings……..

Forward rotating shift patterns can also be described as a phase delaying shift schedule (Tucker *et al*., (2000). This is due to the fact that the rotation of one shift to the next involves a phase delay of the workers circadian rhythm, thereby requiring that the shift worker stays awake for longer.

Backward Rotating Shifts-

On the other side of the coin, backward rotating shifts rotate in the direction of:

Mornings → Nights → Evenings → Mornings........

Backward rotating shifts can also be described as phase advancing shift patterns. This is because the rotation of one shift to the next involves advancing the phase of the circadian rhythm.

Whilst many shift systems employ either one or the other direction of rotation, some shift workers may be required to undertake shift changes that may be in either direction.

Shift systems may be ‘fast’ rotating in which case the various shifts are rotated through quickly (shift change every few days). Alternatively, shift systems may be rotated at a much slower rate, for example a week of nights, or (less commonly nowadays) a month of nights. Some people do permanent night shift work (Ball *et al.*, (2002)).

Shift Work and the Law

In the European Community, working hours are governed by the EC working time directive (93/104/EC), (integrated into UK law as the working time regulations 1998). The directive was introduced as extended working hours and other shift patterns have been shown to be detrimental to health. The directive states the maximum hours that are permitted to be worked, together with the minimum rest periods both whilst on a shift, and also between shifts. The EC working time directive has had a major effect on the way in which some groups can be employed within the healthcare setting in the United Kingdom; for example, in the amount of hours worked by junior doctors.

The Working Time Regulations 1998: Main Points Affecting Shift Workers: (Adapted from 93/104/EC)

- A maximum of 48 hour week (averaged over 17 weeks).
- A minimum rest period of 11 hours between shifts.
- A minimum 20 minutes rest for any work period lasting 6 hours.
- A minimum rest period of 24 or 48 hours per week (averaged over 2 weeks).
- A maximum of 8 hours night work in every 24 hours (averaged over 17 week).
- The provision of free health checks for night shift workers.
- Minimum requirements for paid leave (4 weeks per year).

Studying Shift Work

Shift work studies can be divided into those that are performed in the field (i.e. in the real workplace), and those which are performed in the laboratory (i.e. simulated working environment). Results may be obtained that are a measure of either acute or chronic effects; the latter may require follow up investigation for several years or even decades after the study.

Simulated Shift Work

Some studies have tried to reduce the amount of variables that are present in the normal working environment by running simulated shift pattern experiments (Reid & Dawson, 2001); (Lamond *et al.*, 2003), in which the individuals are closely monitored, and their activities tightly controlled. The drawback here of course is the number of people involved in the studies is low, meaning that is hard to draw statistically significant conclusions.

Reid and Dawson (2001) were comparing the performance of older and younger subjects on a simulated twelve hour shift rotation. The subject's were placed into two groups and then participated in a simulated work shift pattern of two long days followed by two long nights. The main measurement for each of the subjects was the completion of an hourly computer based neurobehavioral assessment task, together with sleep polysomnography. Although the actual working conditions were carefully controlled, there was no indication as to how the subjects were selected. Whilst they found that there was indeed a statistically significant difference between the groups, the fact that there were only 16 people in each group, and that the groups contained both men and women meant that it was probably not controlled enough to draw too many conclusions from the study (due to gender variation and small sample size).

Implications of Shift Work

Shift work, and in particular night shift work, has been implicated in a reduction in work performance (Reid & Dawson, 2001), an increase in accidents (Gold *et al.,* 1992) and detrimental physiological and psychological effects on the worker (Rajaratnam & Arendt, 2001).

The biological reasons behind these are important, and may give an indication to encourage employers to rethink the way in which shift schedules are planned and employees are treated. It may also suggest to the employee how they might be able to minimise risk and detrimental effects. Further research could ensure 'evidence based practice' which could see the development of shift working schedules, based on scientific evidence, that try and minimise the reduction in performance, the risk of accidents and harm to the employee and to those around them.

Shift Work and Health

Shift working has been associated with an increase in a number of health problems. The most commonly associated health problems are sleep disturbances, GI disturbances, metabolic disorders and effects on psychological wellbeing. Increased risk of cardiovascular disease has also been linked with shift work (Boggild & Knutsson, 1999).

While the incidence of health problems in shift workers is not disputable, the mechanisms behind the development of such health problems can vary. Risk of developing most diseases is normally dependent on a range of factors that include age, gender, genetic make up, together with lifestyle and environmental factors. The consequences of circadian disruption due to shift work and their contribution to health problems will be evaluated in the fourth chapter.

Shift Work and Risk of Accidents and Injuries

In recent years the negative side of shift working has begun to be appreciated, or rather acknowledged. As well as reduced productivity, shift work has been implicated in increased risk of accidents and injury. For example, two of the worst industrial accidents in history were due to operational errors during night-time work at both Chernobyl and three-mile island (Mitler *et al*., 1988). In the health-care setting, tiredness may lead to clinical errors of judgement, 'sharps' injuries or drug administration errors.

The scientific study of risk on different shifts is notoriously difficult as staffing levels are often different and activities or duties are not the same during the different shifts. Some studies have attempted to standardize shift work, to try and minimise these factors as variables (Alfredsson *et al*., 1982). There is also the problem of other uncontrollable variations, such as lifestyle factors. Shift work (in the developed western world at least) is often 'selective' in itself in that it will only be undertaken by those who can cope with its adverse effects. It is also often difficult to get a large enough sample size to produce statistically significant results; in some types of study, the population size needs to be extremely large (Folkard, 2004). It may also be inappropriate to suggest that results obtained from different studies are equivalent, due to the nature of the work and other local factors. However, there have been a number of attempts to study, or at least survey the relative risk associated with different shifts. In a study by Smith *et al*., (1994) the relative risk of accidents occurring in an engineering company was found to be 1.23 times higher on the night shift than on the morning shift. This finding was based on the analysis of 4645 injury reports over a period of a year.

Gold *et al.* (1992) surveyed 635 American nurses using a questionnaire. Whilst they found that those who rotated reported a higher incidence of both sleepiness and accidents, the self-administered questionnaire meant that the results were subjective, rather than scientifically informative. For example, it may be argued that the rate of return of questionnaires may be higher in those who have suffered accidents than those who have not.

Shift Work and Performance: Fatigue and Alertness

Fatigue is the most commonly reported health problem associated with shift working. Fatigue results in a loss of performance and concentration, and may also lead to a range of other psychological, physiological and social complications. Lamond & Dawson, (1999) performed a series of experiments in which they compared the effects of blood [alcohol] against the number of hours of wakefulness on task performance. They showed that the mean performance scores in individuals who had been awake for over 24 hours were equivalent to those obtained with blood [alcohol] >1000mg L^{-1} ; the legal limit (in the UK) being 800mg L^{-1} .

Subjective alertness varies over time, with individuals feeling most alert during the morning, with a gradual decline over the rest of the day.

This has implications not only at work, but may also affect the employee’s ability to commute home safely. Loss of concentration due to drowsiness is responsible for more vehicle accidents than drugs and alcohol combined; a recent notable accident was that of the Selby rail crash (2001) in which the motorist who was convicted of causing the accident had not slept for 36 hours before causing the carnage that claimed ten lives.

CHAPTER TWO

INTRODUCTION TO BIOLOGICAL RHYTHMS

Forward

Biology is rhythmic in nature, due to evolution taking place in a world that is defined by repetitive cycling patterns as the earth rotates on its axis (Day/Night), and follows an orbit around the sun (Summer/Winter). Evolutionary adaptation to these cycling environmental factors was therefore a prerequisite for establishing life on earth.

Circadian Rhythms

The rhythmic patterns of biology that follows an almost 24 hour cycle are collectively known as circadian rhythms ('about a day'). A wide variety of physiological processes have been shown to follow this 24 hour cycle. Many of these rhythms are however endogenously generated, and not wholly dependent on external factors. That is, they continue to cycle, or 'free run' with approximately 24 hour incidence in the absence of external cues or stimuli and are therefore determined by endogenous biological clocks. External cues are important for entraining these rhythms to the twenty four hour cycle, the most important of which being light. Figure [1] illustrates a number of physiological rhythms that are circadian in nature. Chapter Three deals with the mechanisms involved in the generation and maintenance of these circadian rhythms, together with the way in which the central rhythm may be entrained by external stimuli.

Ultradian Rhythms

Other biological rhythms (summarised in table [1]) include extremely fast ultradian rhythms whose period are in the region of milliseconds (e.g. nerve impulse) to a few hours (e.g. sleep). Other examples of ultradian rhythms include breathing, BP, and the rhythms that are seen in the electrocardiogram (ECG).

Infradian Rhythms

On the other hand, there are also longer infradian rhythms that cycle over a number of days, the most obvious example being that of the adult female oestrous cycle, which follows a cycle of an average of 28 days. There are many more examples of infradian rhythms in both the animal and plant kingdoms.

Rhythms of Different Period are superimposed on one another

An extremely important idea that needs considering when studying biological systems is that rhythms of different periods are superimposed on top of one another. For example, hormone release is often pulsatile (ultradian), but also follows a slower circadian oscillation of overall release, and this may be influenced by infradian rhythms, such as the oestrous cycle.

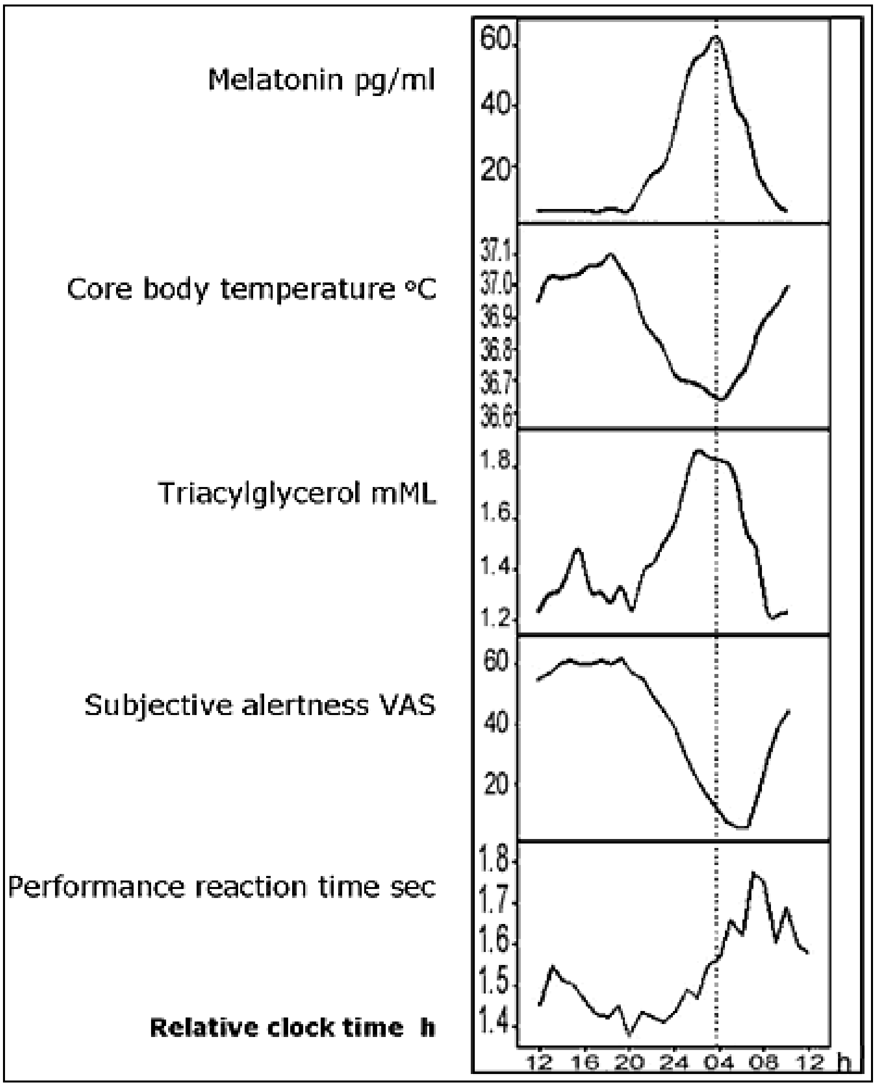
Table [I] Details the period of rhythms that may be encountered

Domain	**Region**	**Period (t)**	**Examples**
Ultradian		t < 20 hr	ECG, BP, breathing
Circadian		t = 24 hr ± 4 hr	Cortisol
Infradian		t > 28 hr	
	Circatrigintan	t = 30 ± 3 days	Female oestrous cycle
	Circannual	t = 1yr ± 3 months	Mating in some mammals

Adapted from: Touitou/Haus (Editors). 1994. Biologic Rhythms in Clinical and Laboratory Medicine. Springer-Verlag. Berlin. Page 7.

Examples of Circadian Rhythms

Figure [1] Some Examples of Circadian Rhythms that are Present in Humans



(Reproduced from Rajaratnam & Arendt, 2001 Lancet Volume 358 Pages 999-1005)

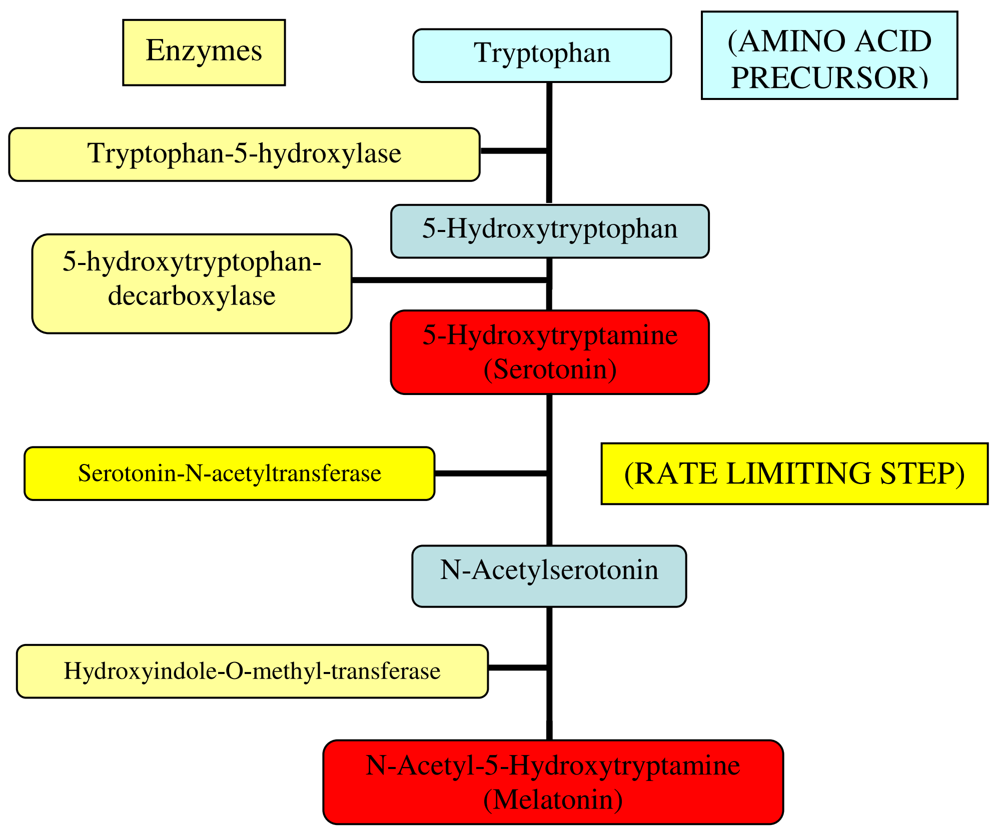
Melatonin

Melatonin (MT) is an indolamide produced by the pineal gland, its synthesis controlled by the SCN, in a manner that is proportional to the duration of darkness. The biosynthetic pathway is outlined in figure [2]. Melatonin acts on target MT1 and

MT2 receptors (both are G-protein coupled receptors), and also on MT3 receptors (a quinine reductase enzyme); (Witt-Enderby *et al.*, 2002).

The excitement regarding melatonin is due to the fact that there is a direct connection between the SCN and the pineal gland, and the fact that melatonin, when measured (in either plasma or saliva) is an extremely reliable indicator of a subject's circadian phase position (Roemer *et al.*, 2003). Its metabolites, notably 6-sulphatoxymelatonin can also be measured in urine.

Figure [2]: Biosynthetic Pathway for melatonin. The rate limiting step (RLS) is the conversion of serotonin to N-Acetylserotonin. This may be either due to the enzyme kinetics or serotonin availability.



Core Temperature

Core body temperature follows a well defined circadian cycle. It reaches a peak during the day and is lowest during the early hours of the morning. The core body temperature reflects the level of metabolic activity within the body at the time. There seems to be a correlation between melatonin secretion and core temperature. (Johnson *et al.,* 1992) examined the relationship between body temperature, short-term memory, performance and alertness. They found that they all oscillated in parallel thereby suggesting that they were controlled by the same pacemaker.

Subjective Alertness

This is greatest during the daylight hours and is lowest during the night time. This is one of the major concerns to the night worker.

Short Term Memory

As described above, short term memory follows a circadian pattern which mimics that of the core body temperature rhythm.

Triacylglycerol

Plasma [Triacylglycerol] follows a circadian pattern, being highest during the night time (Morgan *et al*., 1998) and lowest during the daytime.

Desynchronisation of circadian rhythms due to shift working may have detrimental effects on the workers ability to perform tasks proficiently, and also on their physiological and psychological wellbeing. This is evaluated in chapter four.

CHAPTER THREE

DEVELOPMENT AND MAINTENANCE OF CIRCADIAN RHYTHMS

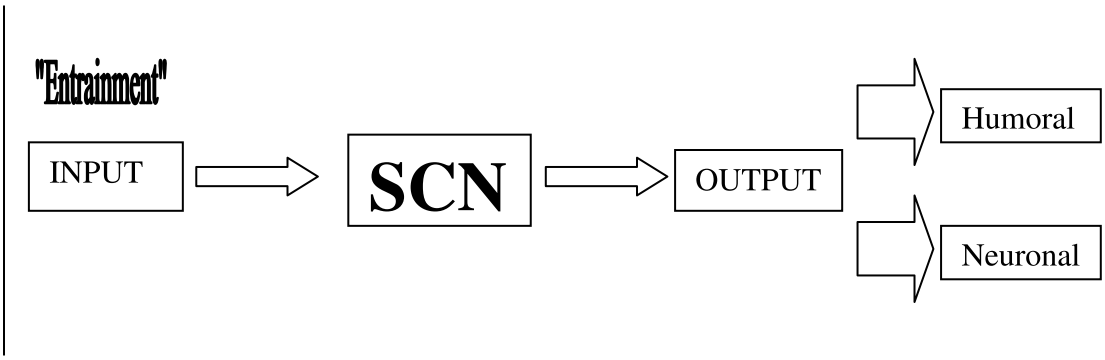
Rhythm Development and Maintenance

In the last few years there has been a great deal of progress into our understanding of the molecular control of the circadian rhythms. A number of genes and transcription factors have now been identified in a number of different species that act as 'biological clocks', thereby controlling these oscillating rhythms. A great deal of the early work has been carried out in the fly *drosophila*; with the mapping of the genes and transcription factors involved (Ishida *et al*., 1999). In true biochemist style, genes have been given names such as CLOCK, TIME, and TIMELESS. Subsequent research has focused on finding homologues of these genes and transcription factors in more advanced species, including man.

The most interesting and perhaps important cells involved in maintenance of the circadian rhythms are those that are located in the suprachiasmatic nucleus (SCN). The SCN is made up of multiple single cell oscillators, which are synchronised by an effect involving the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). This 'master' clock has been shown in mammals to control all other peripheral circadian rhythms. These findings suggest that SCN derived circulating product(s) may well be released, although these have, as of the present, yet to be identified. Further evidence for this comes from studies in the rat (Sakamoto *et al*., 1998) that involved the measurement of a particular mRNA transcript that displays circadian rhythmicity in expression in a variety of tissues. When the SCN was knocked out, by lesion of the SCN area, the rhythmic expression in all tissues was abolished. The gene encoding this mRNA transcript was also found to be a homologue of a gene mapped in drosophila and had already been identified as part of its clock mechanisms.

Recently (Ueyama *et al.*, 1999), a number of multi-synaptic pathways that feed from the SCN in to the sympathetic autonomic nervous system have been mapped in a variety of animals using viral trans-neural labelling. This therefore demonstrates that, in addition to humoral output, the SCN may also mediate its master clock role by neural discharge, particularly involving the autonomic nervous system. The output from the SCN (in very basic terms) can therefore be outlined as in Figure [3],

Figure [3]: Basic Diagram showing Inputs and Outputs from SCN



Other Research: Polymorphisms in Regulatory Genes may affect Phenotype

Katzenberg *et al*. (1998) recently described a CLOCK polymorphism linked to human diurnal preference; that is, morning or evening preference for activity. Their study involved 410 normal adults completing a questionnaire; the answers of which were used to assign individuals into ‘morning’ or ‘evening’ type groups. The alleles were identified by taking advantage of an SNP in the 3’ untranslated region of the human CLOCK gene. This was performed by creating two oligonuceleotide primers which allowed PCR amplification of the complementary region, and then two sequence specific hybridisation probes. They found that there was a statistically significant difference in the scoring of the questionnaire (i.e. diurnal preference) between individuals who possessed a particular allele of CLOCK. This study used modern molecular biological techniques, but used a rather subjective questionnaire to assign groups; this may have limited the validity of the results. For instance, other questionnaires used to determine diurnal preference include 'intermediate' types – this was not an option here. It must be added that it is likely that other genes may also play a role in determining diurnal preference, but this does suggest a genetic basis for diurnal preference.

This therefore raises the perhaps slightly disturbing possibility that one day it may be possible to develop a set of genetic tests which may help to indicate a potential employees 'genetic suitability' for shift work.

Mechanisms of Entrainment

If normal sighted individuals are made to spend long periods of time in total darkness then their circadian rhythms will free run at a period of close to, but not exactly twenty four hours.

Several groups have studied circadian rhythm abnormalities in individuals who are blind (Sack *et al*., 1992); (Klerman *et al*., 1998). Blind individuals seem to have a much higher incidence of circadian rhythm abnormalities than the sighted population. In most of the studies however, the sample sizes were very small, and there was limited details on how subjects were recruited – therefore it would not be correct to imply the clinical implication or actual incidence of these abnormalities in the population; (parallels could be drawn with concluding an association between autism and the MMR vaccine (Wakefield *et al*., 1998) with a study of only 11 'hand picked' children). Sack *et al*., (1992) studied twenty blind individuals and found that nearly all had circadian abnormalities. This, and other studies (involving sighted subjects) have emphasized that light is indeed an important exogenous synchroniser for circadian rhythms. Without this important input the majority of subjects had free running melatonin rhythms. Klerman *et al*. (1998) did however find that some individuals who were totally blind did have some method of entraining their circadian rhythm. To determine this they conducted their investigation in almost total darkness. They concluded that these individuals had a natural circadian period extremely close to twenty-four hours, and that this was close enough for normally less important non-photic entrainment methods to exert a fully entraining effect. These less significant entrainment methods may include physical activity (Buxton *et al*., 1997), as nocturnal activity has been shown to be able to phase adjust circadian rhythms under experimental conditions (particularly in experimental animals). It has been postulated that this (exercise) and other mechanisms may be exploited to help re-entrain circadian rhythms after shift working or long flights; this is discussed in the final chapter.

CHAPTER FOUR

CONSEQUENCES OF DISRUPTION OF CIRCADIAN RHYTHMS IN RELATION TO HEALTH PROBLEMS ASSOCIATED WITH SHIFT WORK

Forward

Disruption of Circadian Rhythms produces a variety of physiological and psychological problems for those who participate in shift work. These were mentioned in the first chapter. This chapter evaluates why these problems may occur by examining the relationship between circadian disruption and the physiological and psychological problems that have been associated with shift work.

Studying Disruption

Studying the consequences of circadian disruptions due to shift work is a relatively recent type of study. A well designed study is extremely important in order to be able to draw any meaningful conclusions. It is therefore important to minimise all of the variables, and, if comparing the results of several studies to understand that different methods can produce very different results. Taking for example a study to determine the level of circadian disruption due to feeding activity. Any results may be the sum of a great number of factors. Firstly, there is the individual variation (age, gender, BMI, fitness). Secondly, there is the type of shift work being studied (and whether or not the individuals taking part have done these shift patterns before). There is also the timing and/or frequency of feeding, together with the nutritional and calorific content of each of the meals. Other lifestyle and environmental factors also need to be carefully considered. All this, added to the fact that these types of investigations are time consuming and expensive means it is therefore unpractical to perform on large numbers of participants, and this therefore reduces the statistical significance of any resulting conclusions. This therefore means that data from small scale studies must be used, but emphasizes the importance of good study design.

Food Consumption and Absorption

Response to food intake has been shown to vary depending on the timing of meals and also to the content of the meal (Holmback *et al*., 2002). Part of this variation has been explained by the fact that the rate of gastric emptying varies over the course of the day, and also that different food contents are digested at different speeds. Timing of feeding during shift work may be linked to GI disturbances and also metabolic disorders, both of which have been associated with shift work (Knutsson, 2003).

Effects on Metabolism

Metabolism of both food products as well as drugs has been shown to follow a pattern of circadian rhythmicity.

One reason as to why shift workers may fail to adapt to altered circadian patterns is an effect mediated by an inappropriate response to meals by the endocrine system and metabolic machinery, whilst working on the night shift (Ribeiro *et al.*, 1998). Several small studies have been carried out in order to investigate whether there are indeed abnormal responses to feeding during the night time.

Carbohydrate Metabolism

Weibel & Brandenberger, (2000) studied the ultradian and circadian rhythms of glucose and insulin in permanent night shift workers compared with those seen in normal 'daytime' workers. In humans insulin is secreted in a complex pattern characterised by rapid pulses every ten or so minutes superimposed on oscillating fluctuations of a period of one and a half to two hours (Cauter *et al*. (1997). Weibel & Brandenberger, (2000) found that even in permanent night workers, the circadian rhythms of glucose and insulin never managed to fully adapt to the night working shift schedule.

The point here is that permanent night shift workers are the group of individuals who are most likely to adapt their circadian pattern to match their imposed working hours. If they cannot fully adapt to this permanent change, then those who have rapidly rotating shift patterns are even less likely to adapt, and this may explain some of the common symptoms of metabolic disorders associated with shift work.

Shift work and Metabolic Disorders

There are only a small number of epidemiological studies looking at the incidence of diabetes and other endocrine disorders in shift workers compared to the general population, and none of these were performed in the health care setting. In a relatively old Australian study (Koller *et al*., 1978) endocrine disorder incidence was found to be at 3.5% in night shift workers compared to 1.5% in day time workers at an oil refinery (n=300).

Mechanisms

Diabetics may be at particular risk when working shifts. This is because their meal routine will be seriously disrupted, and it may be extremely difficult to judge the correct amount of insulin to take. Severe diabetes may be reason enough to exclude some workers from rapidly rotating shift work, and sufferers may exclude themselves from this type of shift working.

Lipid Metabolism

Holmback *et al*. (2002) showed that the circadian rhythms of lipid metabolism were disrupted by nocturnal feeding. They found that oxidation of fats and heat release could be displaced by consuming meals of high fat (but not high carbohydrate) content during the night. Nocturnal [TAG] was shown by Morgan *et al*. (1998) to be affected by disruption of sleep during the night, which is seen in shift workers. The disrupted rhythms of lipid metabolism that are seen in shift workers may be linked to the increased risk of cardiovascular disease (Boggild & Knutsson, 1999).

Drug Metabolism

The metabolism of many drugs has been shown to follow circadian rhythm.
Some drugs, for example the cholesterol reducing statins (e.g. Atorvastatin) have been shown to be more effective when administered in the evening (Wallace *et al*., 2003). This is thought to be due to the fact that cholesterol synthesis is greatest when dietary intake is lowest. Parameters for this (and other types of drug that show circadian variation in action or metabolism) may therefore be different in those who work and eat during the night shift (Holmback *et al*., 2002).

The Cardiovascular System and Shift Work

In the late 1970s the consensus amongst experts that that there was no evidence to suggest a correlation between shift work and cardiovascular disease. Over the past twenty-five years several studies have undermined this consensus. There have been a variety of studies looking at the risk of cardiovascular disease and work patterns (Alfredsson *et al*., 1982); (Knutsson *et al*., 1986 & 1999).

Boggild & Knutsson (1999) reported a 40% increase in risk of developing cardiovascular disease in shift workers compared to the general population. They evaluated data from a number of large scale cross-sectional studies, and also case-referent studies. Not all of the studies showed that there was indeed a relationship, although this was probably due to the fact that the studies all had different designs and methods.

Steenland & Fine (1996) carried out an epidemiological study to see whether rotating shifts (as compared to fixed shifts) increased the incidence of cardiovascular disease at work. They did not find any indication that workers involved in rapidly rotating shift work were at greater risk than those who were on permanent shifts. However, this may have been due to the fact that the numbers of individuals who rotated shifts in their study was very small compared to the total sample size.

<u>Mechanisms</u>

The Cardiovascular system is modulated by both internal and external signals in order to maintain an effective blood supply to the body. There are complex interactions between a wide variety of both endocrine and nervous signalling pathways, many of which follow circadian rhythmicity. Young *et al.* (2001) showed that the heart has intrinsic circadian rhythms. They showed this by working with isolated rat hearts that were devoid of nervous innervation or humoral factor stimulation. Their work showed that a number of metabolic genes were expressed in a circadian pattern, the peak of which was in the night. They also found that in the hypertrophied heart, this intrinsic rhythmic expression was abolished. This therefore meant that the hearts were not able to adjust to the varying physiological demands and conditions that are associated with different times of the day. It could therefore be speculated that shift work may interfere with the metabolic regulation that is meant to occur in the heart at a particular time of day, for instance during the night. For example, the heart is normally exerted to a greater extent during the day and may reserve some metabolic 'housekeeping' activities for the time when it is under less exertion (during the night); an analogous situation may be that of the brain utilising sleep as a period of consolidation. Being active during the night may disrupt these processes and therefore increase the risk of developing cardiovascular disease.

Furlan *et al*. (2000) investigated the interaction between shift work and the autonomic nervous system in 24 male subjects over a period of three shifts. The autonomic nervous system had already been shown to undergo circadian oscillations of discharge, and has outputs from the SCN (Ueyama *et al*., 1999). In their study they found that when workers were subjected to continuous alterations in shift patterns this resulted in a disruption of the balance between autonomic and vagal innervation of the heart, with a statistically significant reduced sympathetic autonomic component seen during night shift. This, they concluded, may have a bearing on the alertness of the worker during the shift, and may also partly explain the increased incidence of cardiovascular disease in these workers.

Blood Pressure

Blood pressure shows diurnal variability, as well as minute to minute variation. Baumgart *et al*. (1989) investigated how the diurnal variation in blood pressure was affected by shift work and circadian position. They found that there was no difference between mean twenty-four hour BP in individuals working either day or night shifts. This therefore suggested that BP was related to activity rather than the influence of circadian rhythms. This study however was small in size (n=17), and sleep in some of the individuals was disturbed by the activity of the automatic blood pressure monitors (which took a reading every thirty-minutes).

Kario *et al*. (2001) reported an association between certain forms of diurnal blood pressure variation and what they described as 'negative effect'; such as depression, anxiety and sleep quality in a group of 231 working males and females. They found that disrupted diurnal variation in blood pressure was associated with depression in males, whilst disrupted awake BP and PR may be associated with anxiety in females. Whether these associations may be present particularly in shift workers was not reported. However, this study did show that variation in BP may not just be dependent on physical activity (Baumgart *et al*., 1989); there may also be a substantial psychological component. It may have been wise to measure plasma catecholamines and cortisol, which are both markers of stress. This is what Goldstein *et al*. (1999) carried out in one of the few published studies to focus on female nurses (n=138). HR and BP, together with urinary catecholamines and cortisol were monitored for four days (two days of work, followed by two days off work; all participants were in the luteal or follicular phases of their menstrual cycle) Whilst they found that BP and HR were both increased during working hours, other social factors also had a major influence on the difference between days on and off, and also on the urinary catecholamines and cortisol.

Heart Rate Variability (HRV) and Premature Ventricular Complexes (PVCs)

There have been several studies into whether shift work increases heart rate variability. One such study (Amelsvoort *et al*., 2001), compared the frequency of PVC's in a population of workers after completing one year of night shifts. Their study found that the night working group displayed increased frequency of PVC's compared to the alternative group, which worked only day shifts. They did not however find a statistically significant increase in HRV in shift workers over the period of study.

It could therefore be postulated that the increased generation of arrhythmias (PVC's) may contribute towards increased risk of cardiovascular disease in shift workers.

Behavioural and Emotional Responses to Shift Work

The most common of all health problems that are associated with shift work are those affecting mood and behaviour. These may affect not only the shift worker, but also those around them. The trouble with trying to measure behavioural and emotional responses is the fact that they are very subjective in nature and it is difficult to quantify the component value of each; for example low mood may be due to shift work, or it may also be due to other life stresses.

<u>Stress</u>

Stress is a subjective psychological measure that may have a number of components. It also has some physiological markers, such as elevated [cortisol] and [epeinepherine]. Whilst some studies use subjective questionnaires to determine stress levels, others rely on these physiological markers; some incorporate both types of data.

Staying Awake and Insomnia

Part of the problem with shift work is the psychological battle of trying to maintain awake, when the body really thinks that it should be sleeping. Many shift workers report that this is a particular problem in the first few night shifts. This problem declines as the circadian rhythms are adjusted over a number of days. It is then a problem at the end of the shifts, when the body expects to sleep during the day.

Pain and Shift Work

Certain types of pain are often reported to cause problems during night shift work. For instance, common complaints are joint and back pain flaring up during the night shift.

Mechanisms

This may be explained, at least in part, by the fact that cortisol secretion is lowest during the night time. Cortisol plays a role in preventing inflammation, possibly by inducing lipocortin which then inhibits the cyclo-oxygenase (COX) pathway. This pathway normally results in the formation of a variety of inflammatory mediators (e.g. prostaglandins). COX inhibitors (e.g. Ibuprofen) may be of benefit in these instances. Another factor is that pain is a subjective experience, and may appear to be worse due to the mood of the worker being at a low, which is the natural case during night work.

Other Endocrine Responses to Shift Work

Oestrous Cycle

The oestrous cycle is an additional complication that is superimposed onto circadian rhythms in women. The interaction between the two is complex, and is the main reason that most investigational studies exclude women, or specify that the women must be at a set stage of their oestrous cycle.

While many women complain of pre-menstrual tension, the additional endocrine disruption associated with circadian disruption (i.e. during shift working) may add to their physiological and psychological complaints during this time.

Testosterone and Cortisol

An interesting recent paper by Axelsson *et al.* (2003) measured changes in testosterone, cortisol and prolactin in two groups of shift workers. One group had been classified as satisfied with their work schedule, whilst the second group were classified as being dissatisfied. They found that those who were dissatisfied had lower morning plasma [testosterone] than those who were satisfied. They also linked the low morning [testosterone] to disturbances in sleep-wake cycle and slower recovery after finishing a shift rotation. This may therefore suggest one of two possibilities. Firstly, that plasma [testosterone] may influence the psychological parameters of the male night shift worker, or secondly, it may just indicate that this rhythm is disrupted differently in individuals that are less satisfied with night working. Further studies would be required to determine cause and effect.

Temperature

Reinberg *et al*. (1984) investigated the relationship between the disruption of the temperature circadian rhythm and the development of intolerance to cope with shift working. They used clinical signs as a means of determining intolerance, such as measures of sleep disturbance, psychological complaints and GI problems. Their study found that while individuals who were able to tolerate shift work did not lose their temperature circadian rhythm, individuals who displayed intolerance had a much greater tendency to having a free running rhythm. This was corrected in individuals when they returned to normal diurnal working patterns.

CHAPTER FIVE

TREATMENT AND ADAPTION STRATEGIES

Forward

Shift work is a necessity in the healthcare environment in order to provide effective care and treatment to patients. It is also necessary in many other workplaces and industries. Unfortunately, shift work may create a wide range of problems; these have been discussed above. This final chapter evaluates the methods and adaptation strategies by which shift workers and their employers may be able to minimise disruption to their psychological and physiological wellbeing, and at the same time minimise risk of accidents and declines in performance.

Personnel Selection: 'Morning-types and Evening-types'

There is a substantial quantity of literature to support the fact that there are indeed two distinct groups of people with regards to diurnal preference; there are those who prefer to be active in the morning (larks), and those who prefer to be active in the evening, (owls). Several explanations have been given as to the basis of this. There is some evidence suggesting a genetic basis for this (Katzenberg *et al*., 1998) – see chapter three. There may also be social and/or other factors which influence an individual's diurnal preference.

Wallace & Fisher, (2001) suggested that diurnal preference may be dependent on the time of birth of an individual! The authors suggest that the amount of light at birth may be factor in determining the subject's diurnal preference in later life. This is somewhat puzzling as the majority of births occur indoors under artificial light;

perhaps a more plausible suggestion may be due to the circadian phase position of the mother during labour. Whatever the mechanism, there are definitely individuals who can best cope with staying up late, and another group who naturally rise early. It may be possible to select individuals for shift work based on their answers to specific questions in interview or assessment.

In many cases, shift work will naturally select those who are able to cope with its effects. This however is probably less true in the healthcare setting, as doctors and nurses are generally expected to participate in shift working during their junior years.

There has been considerable debate in the UK as to whether nurses or other workers should be forced to work night shifts. Night shift work is one of the principal factors causing dissatisfaction in the nursing profession, and is often a contributory reason as to why some leave the profession (Palmer, 2003); (Ball *et al*., 2002). This could ultimately end up as a legal issue, as if it is possible to show that shift work produces physiological or psychological harm or distress in some individuals, then it may be argued that an employer has no right to force those affected to work such a regime.

<u>Personnel Exclusion</u>

Certain groups of people should perhaps be excluded from participating in shift work. One such group may be those who suffer from epilepsy. Epileptics may be at increased risk of seizures, as these may be triggered by sleep deprivation and fatigue. Those who suffer from nocturnal asthma may also be at greater risk when working during the night time (although in the healthcare setting it is preferable to have an attack in hospital rather than at home).

Shift and Sleep Patterns

Shift Patterns

Several studies have been carried out to determine whether one type of shift pattern is more appropriate than another with regards to negative effects and performance. Tucker *et al.* (2000) carried out a study looking at the effects of direction of rotation of shifts on a range of measures. They found that there was not a great deal of difference in 'effect' between the different rotating patterns, although forward rotating patterns were associated with a greater decline in alertness across the shift compared with those participating in the backward rotating pattern.

Wilkinson (1992) produced a comprehensive review on the subject of 'how fast should the night shift rotate?' In this review he argued that some so called 'expert opinions' on the matter were not based on scientific evidence. His review included collecting empirical data from studies that recorded the number of hours of sleep that subjects managed to achieve when working either permanent nights, rapidly rotating, or weekly rotating shifts. For permanent nights, the average from 18 studies was 6.72 hours; whilst for weekly rotating nights (from 17 studies) the average was 6.30 hours. For rapidly rotating shifts the duration was 5.79 hours (from 9 studies). There was however considerable differences in the occupations, size and ages of the groups. An important factor that may cause one to question the results of some of the studies is that in the majority of cases the sleep recording was by means of a sleep-diary or log, which is in itself a very subjective measure. A better, more modern approach would be the use of a sleep polygraph recorder.

To sum up, rapidly rotating shifts may result in a build up of fatigue due to loss of sleep, compared to slower rotating shifts.

Designing Shift Schedules

The designing of shift schedules is troublesome in that it is a balance between several factors. Whilst fast rotating shifts allow individuals to perform more normally on days off (for example, have a social life), it also means that on the night shift they are more likely to suffer from fatigue and have a greater reduction in alertness and performance. On the other hand, slower rotating schedules mean that workers become better adapted to the night shift, and they will therefore be more alert during the shift. The downside this time is that they are less able to function (on a social level) on their days off. It is ultimately a question of whether the shift system is designed on the pretence of working to live, or vice versa. Other factors that need to be considered are the need to cover shifts with a finite pool of workers, and the need to comply with the EC working time directive (see chapter one).

Shift Length

With regards as to which shift system is best in terms of shift length, there is data to support both normal (seven or eight hour) shifts and double (twelve hour) shifts (Smith et al., 1998). Again it is a case of balancing the positive and negative factors. Double shifts are associated with increased tiredness whilst on duty (particularly during the end of the shift), which may therefore increase the risk of accidents. However double shifts mean that the worker needs to work fewer shifts, and therefore has more time to enjoy life on their days off. This increased enjoyment may outweigh the negative factors for many individuals (certainly, double shifts have become increasingly common). To conclude, there is no reason not to use double shifts if the worker is allowed to have adequate breaks.

Sleep Patterns

Sleep patterns have been shown to play a role in entraining circadian phase. This has been described as 'anchor sleep' (Minors and Waterhouse, 1983). Short naps during a shift have been suggested to be of possible benefit, although there have as yet been no studies to substantiate these claims, although there are currently unfinished studies being performed in Japan.

Sleep before air travel to Australia was shown to be a factor in the level and duration of jet lag in a group of athletes and other people studied by Waterhouse *et al*., (2002). They found that the pattern of sleep in the twenty four hour period before flying had a significant effect on the duration of jet lag that was experienced in the study group. The trouble is that sleep patterns are often dictated to the shift worker, due to social obligations, and it is not always possible to determine sleep duration before starting shifts. Adequate sleep is however necessary to ensure that a sleep debt is not built up over shifts, and to minimise fatigue.

Light Entrainment

There have been numerous attempts to try and determine whether bright light administered at the appropriate time can be used entrain the circadian rhythms High intensity light has become popular in recent years to treat seasonal affective disorder (SAD), where it has proved to have efficacy. The effectiveness of this treatment may be due in part to the finding that in some types of depression, circadian rhythms of hormones such as cortisol are disrupted.

Both Eastman (1992) and Boivin & James (2002) demonstrated that bright light (with an intensity >2000 lux) administered during shift working has a number of effects. Firstly, it suppresses melatonin secretion. This produces a rise in core body temperature and an increase in alertness. Most studies have shown that bright light may phase shift circadian rhythms. While a number of different studies have been performed, the light intensities used ranged from 2000 lux (Boivin & James), up to 7000-12000 lux (Czeisler *et al*., 1990). They do all however provide evidence to support the use of bright light as a treatment for maladaption to shift work.

Although light of intensity >2000 lux (administered at the correct time) has shown to have a positive effect on night workers, it's intensity is too great for it to be able to be used on a ward at night in a hospital setting (normal light bulbs emit light of intensity < 500 lux). It may however be possible to administer it in special areas, or in the home.

Lushington *et al*. (2002) carried out a study to see whether extraocular light exposure whilst subjects were asleep had any effect on entrainment of circadian rhythm. This, they suggest could be an effective solution to certain circadian rhythm disorders as the treatment could be administered during sleep. Unfortunately they did not find that extraocular light did have any effect (except that in some subjects wakefulness was increased). These findings support those by Sack *et al.,* (1992) that it is indeed light signal via the ocular route that entrains the circadian rhythm. Visser *et al*. (1999) investigated the level of melatonin suppression depending on the area of the retina that was exposed to the light. They reasoned that in animal studies there was uneven distribution of ganglia connecting the retina and SCN. Their very small (only 8 subjects) study suggested the density was greatest from the nasal part of the retina, as suppression was greatest when this part of the retina was illuminated.

To sum up, high intensity light has a beneficial role to play in phase adjusting circadian rhythms in shift workers.

Darkness

Light avoidance at critical times in the circadian cycle has been shown, in at least one study (Boivin & James, 2002) to be effective at avoiding further circadian disruption. Certainly, day time sleep quality is often reduced by sunlight coming through inadequate curtains (together with day time noise, as already discussed). Darkness may be administered either using 'black out' curtains or blinds, or the use of a blindfold (Eastman, 1992). By applying the principles above, it may be a possibility that if individuals could avoid all bright light in the morning after a night shift, then they may find it easier to sleep, and may also suffer less circadian disruption. This would be due to the knowledge that bright light is the most important exogenous entraining stimuli. This may not however be a practical suggestion.

Pharmacological Intervention

Wake-Enhancing Drugs

Caffeine has long been used to aid shift workers to maintain a state of wake and alertness. This is reflected in the culturally adapted timing of drinking tea and coffee (in the morning and afternoon – as drinking in the evening may prevent sleep. Its mode of action concerns antagonism of adenosine A1 receptors and possible other modulatory effects on phosphodiesterases. Several studies have been conducted in both normal and individuals who have been deprived of sleep. Lieberman *et al* (1987) found that even small doses could be shown to increase performance in normal subjects; although other studies have been less positive.

Caffeine itself is not free from side effects; repetitive usage produces mild dependence (and withdrawal can produce mild withdrawal effects). Excessive use has been associated with anxiety and headaches.

Amphetamine has been experimented with, but is unsuitable due to its psychological effects and also because it causes tolerance and dependence.

More recent drugs include Modafinil, another central adrenergic stimulant. This has been used experimentally in the treatment of narcolepsy and other sleep disorders. There is limited data for its effects on the normal population, and even less on its use in sleep deprived subjects. However, the limited studies that have been conducted show efficacy (Bensimon *et al*., 1989), but this decreases after repeated administration. Other, larger studies in both monkeys (Lagarde *et al*., 1990) and narcoleptic individuals (Bastuji *et al*., 1988) have highlighted that the drug seems to have low toxicity and low incidence of side effects. It does however remain unlicensed in many countries.

To conclude, caffeine is a legal stimulant that has been shown to promote wakefulness, although excessive doses may lead to side effects. There is not enough supporting data to support the use of other wake-enhancing substances within the workplace.

<u>Sleep Aids</u>

Sleeping in the daytime can be a serious problem, and have serious detrimental effects on the quality of sleep of night workers. To start with, there is a greater amount of noise from the environment (this is particularly true in cities with all the traffic). Sunlight may also make it difficult to sleep. There are also physiological reasons why sleeping in the day is harder, for instance, the adrenergic system is active, in anticipation of activity (Burgess *et al*., 1997). Core body temperature is also increased, again as the body gets geared up to function. Urine formation is also greater, meaning that the bladder will fill more rapidly. Obvious non-pharmacological aids to better daytime sleep are good sound insulation, and thick black-out curtains. Nicotine, Caffeine and other stimulants should also be avoided before attempting to sleep.

The Benzodiazepines (e.g. Temazepam) and the newer related drugs such as Zopiclone are used normally on a short term basis to aid sleep. They have proved clinical efficacy, but may produce unwanted effects into the next day or night. Importantly benzodiazepines can disrupt memory formation. Therefore, it would be best to suggest that pharmacological sleep aids are best avoided by the shift worker. The emphasis should instead be placed on improving the sleeping environment.

Exogenous Melatonin

The role of endogenous melatonin and its targets have been discussed in chapter two. The use of melatonin as an aid to improve sleep and reset the circadian clock has been extensively researched in recent years. In countries where its sale is not restricted (as it is in the UK), its usage is common, for both an aid to sleep and also to relieve symptoms of 'jet lag'. Some of its so-called uses are backed by lay press coverage and reports rather than hard scientific evidence.

Conflicting reports as to whether exogenous melatonin can or cannot shift the relative circadian phase position have been published. Hao & Rivkees, (2000) carried out studies in baboons using doses similar to those used in humans to treat human circadian disorders. Their study suggested that administration of melatonin did not shift the circadian phase. However, in a separate placebo-controlled study (n=32), this time in humans, Sharkey & Eastman, (2002) found that melatonin could cause a significant shift in circadian phase; the size of shift being dependent on the dose of melatonin.

It may be that the difference in results between the studies was due to interspecies differences, or it may be due to the difference in experimental design; it is certainly a great deal more difficult to control variables in humans rather than laboratory animals. If melatonin really does shift circadian phase, then its administration to shift workers may be a plausible means to reset the circadian clock. However it is likely that the dosage and timing of dose would need to be carefully considered to avoid further disruption. There is also the point as to whether exogenous melatonin administration had an phase shifting effect that was great enough in size as to overcome other natural phase shifting or entraining factors that would be met by a shift worker in the natural environment; the most obvious and influential being sunlight (this was missing, by design, during the studies). The influence of these would warrant further investigation before deciding whether the use of melatonin in shift workers would be of any practical benefit.

CONCLUDING REMARKS

To conclude, shift working is unfortunately a necessity in the modern society that we live in. There is no ‘ideal’ or even ‘good’ pattern of shift working. However shift schedules can be designed that minimise the build up of fatigue and continual circadian disruption. These need to be balanced against social and other factors. The shift worker can also adopt certain strategies in order to minimise the build up of fatigue and maximise circadian adaptation and re-entrainment. Other strategies and treatments may be available in the future. As there is increasing evidence to suggest that some types of shift work are associated with health problems there may be calls for the revaluation of how much compensatory payments (i.e. ‘unsociable hours’) are made to those working these shifts. Compulsory night shift work may also be a breach of health and safety and human rights regulations. Further studies would be of benefit, particularly in women and in the health care environment, although any studies would need to be carefully designed, with a minimum reliance on subjective data.

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APPENDICIES

Appendix I: Journal Sources

American Association of Occupational Health Nurses Journal (P)
American Journal of Industrial Medicine (P)
American Journal of Physiology (G)
American Journal of Physiology, Endocrinology & Metabolism (G)
American Journal of Public Health (P)
British Journal of Sports Medicine (P)
British Medical Journal (G)
Cell (G)
Chronobiology International (I)
Circulation (G)
Circulation Research (I)
Endocrine Reviews (C)
Ergonomics (I)
Growth, Genetics and Hormones (O)
Hypertension (G)
Industrial Health (I)
International Archives of Occupational and Environmental Health (I)
Journal of Applied Physiology (G)
Journal of Biological Chemistry (P)
Journal of Biological Rhythms (I)
Journal of Endocrinology (G)
Journal of Nutrition (P)
Journal of Sleep Research (I)
Life Sciences (G)
Military Medicine (P)
Nature (G)
Occupational & Environmental Medicine (I)
Occupational Medicine (P)
Proceedings of the National Academy of Sciences (G)
Scandinavian Journal of Work & Environmental Health (I)
Science (G)
Sleep (B)
Social Science Medicine (P)
The Journal of Clinical Endocrinology & Metabolism (P)
The Journal of Social Psychology (P)
The Lancet (G)
The New England Journal of Medicine (G)
Trends in Neurosciences (C)

Key
C = Clifton
B = Boots Library
G = Greenfield Medical Library
I = Inter Library Loan Service
P = ProQuest Medical Library
O = Online (Published on Internet)

Appendix II: Avenues of Research & Methods

Print Libraries Visited:

Clifton Library
Nottingham Trent University,
Clifton Lane,
Nottingham

The Boots Library
Nottingham Trent University
Shakespeare Street
Nottingham

Greenfield Medical Library
University of Nottingham,
Queens Medical Centre,
Derby Road,
Nottingham

Inter-Library Loan Service

Internet Search Engines
www.google.com

The following were accessed through the MyAthens (http://www.athensams.net/myathens/) portal using either an NHS employee account or university access:

ProQuest Medical Library (http://proquest.umi.com/)

British Medical Journals (http://www.bmjjournals.com/)

Highwire Medical Library (http://highwire.stanford.edu/)

Science Direct (http://www.sciencedirect.com)

Internet sites (All addresses correct and verified @ March 2004)

The National Health Service (http://www.nhs.uk/)
(Official website of the NHS)

Department of Health (http://www.dh.gov.uk)
(Official website of the DOH)
Government (http://www.ukonline.gov.uk/)

National Statistics (http://www.statistics.gov.uk/)
(Official government statistics)

Her Majesties Stationary Office (Legislation)
(http://www.legislation.hmso.gov.uk/legislation/uk.htm)
(HMSO's online publishing of UK legislation)

European Union
(http://europa.eu.int/index_en.htm)
(Official portal to European Union)

Nursing & Midwifery Council (http://www.nmc-uk.org/)
(Statutory regulatory body for nurses and midwives in the United Kingdom)

Royal College of Nursing (http://www.rcn.org.uk/)

British Medical Association (http://www.bma.org/)

General Medical Council (http://www.gmc-uk.org/)
(Statutory regulatory body for doctors in the United Kingdom)

UNISON (http://www.unison.org.uk/)
(The official website of United Kingdoms largest public sector trade union)

Other Sources:

The Occupational Health Centre
Queens Medical Centre
Derby Road
Nottingham