# CHRONOBIOLOGY AND PSYCHIATRY:

## Development of a conceptual model and integrative approach for South African Psychiatrists.

**Dissertation submitted to the University of Cape Town Faculty of Health Sciences for the degree of M Med (Psych) Part 3**

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# ABSTRACT

**Chronobiology developed slowly after it was recognised that rhythmicity was a fundamental property of life. However, the principles of chronobiology are not well integrated in clinical practice. Therefore, this dissertation aims to integrate neuroscientific knowledge in a curriculum for chronobiology to be presented to South African psychiatrists in training at UCT, and is one of several steps in a programme to promote the concept of chronobiology in psychiatry.**

*All life has its seasons and cycles, and no one's personal*
*chaos can be permanent.*
*Winter, after all, gives way to spring and summer,*
*Though sometimes when branches stay dark*
*and the earth cracks with ice,*
*One thinks that spring and summer will never come...*
*... but they always do.*

*--Truman Capote*

# CHAPTER 1

# INTRODUCTION

Considering that the human brain consists of approximately 100 billion neurons with 100 trillion neuronal synapses and is submersed in a "soup of neurochemicals"(1) (2), one can appreciate the immense possibilities for pathology. Mathematics (combination theory) allows us to calculate the possible number of permutations (N!) of "N" number of things : i.e. N! = Nx (N-1) x (N-2) x (N-3) x... x 3 x 2 x 1 (3).

Our current understanding of psychiatric disorders is that they have heterogeneous underlying neuropathology expressing themselves through common final pathways. It is then understandable, taking the above mathematical, anatomical and neurochemical realities into account, that psychiatry as a medical specialty will continue to contribute to the evaluation, investigation, treatment and research of individuals presenting with psychiatric symptoms.

Despite continual development in neuroscience our knowledge of the mind's relationship to cerebral excitation remains an enigma. "It is believed that it is not the quality of the sensory nerve impulse that determines the diverse

conscious properties, but rather the different areas of the brain into which they discharge" (4).

The role of hormonal activity in "emotional life" is currently also studied – and although we have little understanding of specific hormonal patterns relating to this the possibilities for speculation and experimentation are vast(5).

Chronobiology developed slowly as a science, but it is now well accepted that rhythmic activity is a fundamental property of living matter (6).

The aim of this dissertation is to, initially, highlight the photoneuroendocrine system in the central nervous system and to develop a conceptual model for the role of chronobiology in psychiatric disorders. The latter will be achieved by integrating relevant neuroscientific knowledge into a core curriculum, relevant for South African psychiatrists and all those in training. Ultimately, however, the aim is that through this effort the teaching of chronobiology be promoted and research on the topic be stimulated, eventually leading to the development of cost effective treatment of psychiatric disorders with underlying chronobiological pathology. Presentations on this topic by the candidate will also be summarized in an addendum.

# CHAPTER 2
# ENDOGENOUS BIOLOGICAL RHYTHMS

## 2.1 Introduction

Endogenous biological rhythms are generated within an organism. They can be categorized as simple or circa ( Latin. circa : about ). Simple endogenous rhythms are not synchronized with external environmental stimuli (e.g. cardiac cycles). Circa endogenous rhythms, however, are influenced by geophysical environmental cycles. Many circa-rhythms are recognised and are called e.g. circatidal ( about 12 hours ), circadian ( about 24 hours ), circalunar (about 28 days ) and circannual ( about 1 year ) (7).

Because of the importance and marked predominance of biological rhythms of "about 24 hours" (circadian ) in eukaryotic organisms, other endogenous rhythms are related to this - ultradian rhythms ( shorter than 24 hours ) and infradian rhythms (longer than 24 hours ) (7)(8) . See Figure 1.

## 2.2 Chronobiology

Chronobiology is defined as the study of mechanisms and alterations of each organism's temporal structure under various situations (6), or as the scientific study of the effect of time on living organisms (9). In order to discuss how chronobiology can contribute to our understanding of its role in psychopathology, it is necessary to elaborate on the concept of biological time structure.

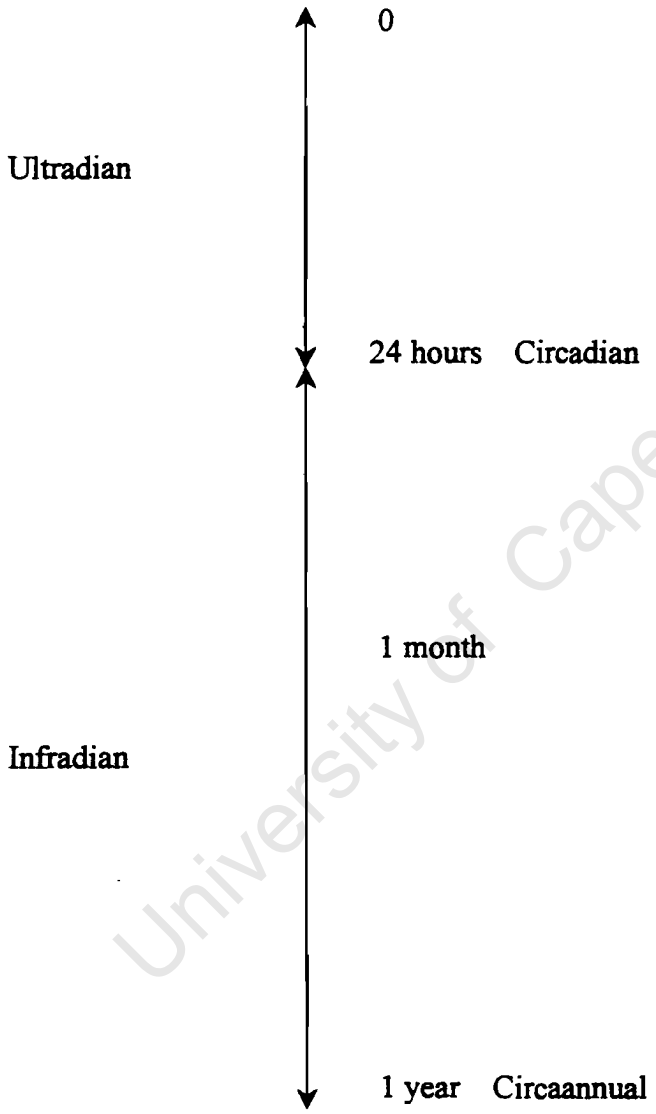





Figure 1 : The relationship between certain biological rhythms. (7,8)

The concepts of anachronobiology ( constructive effects of time on a living system ) and catachronobiology ( deleterious effects of time on a living organism )(9) also become relevant when considering the role of chronobiology in psychopathology.

Biological systems possess a prominent temporal structure. Although the two best known biological rhythms are those with bioperiodicities of about 24 hours (circadian) and about one year ( circannual ), certain biological functions may have other bioperiodicities (6).



2.2.1 The Suprachiasmatic Nucleus

The development of the concept of a biological clock has led to a search for the body's "master clock." It was established that the suprachiasmatic nucleus (SCN) is likely to be the circadian oscillator system, which drives some neuro-endocrine circadian rhythms. This is sometimes called the "y" oscillator (6).

The SCN is a group of about 10 000 neurons located above the optic chiasma, centered around the midline, approximately 3 cm behind the eyes. It is part of the anterior hypothalamic nuclei (10) (11). The SCN, as a hypothalamic structure, is derived from the diencephalon (12), and the

hypothalamus as part of the limbic system (13) has an important role in the genesis of emotion.

The SCN is a member of the photoneuroendocrine systems (6). Via the retinohypothalamic tract, the SCN receives optic input from the environment that is used in the control of biological rhythms and neuroendocrine functions (14).

Other neuronal pathways are also involved in the entrainment of the SCN to the light/dark cycle. It was shown that neurons from a subdivision of the geniculate - an area called the intergeniculate leaflet - also project to the SCN (geniculohypothalamic tract: GHT )(15).

Damage to areas that spare the GHT but involve either the primary optic tracts or the lateral geniculate complex also disrupt the circadian entrainment (15).

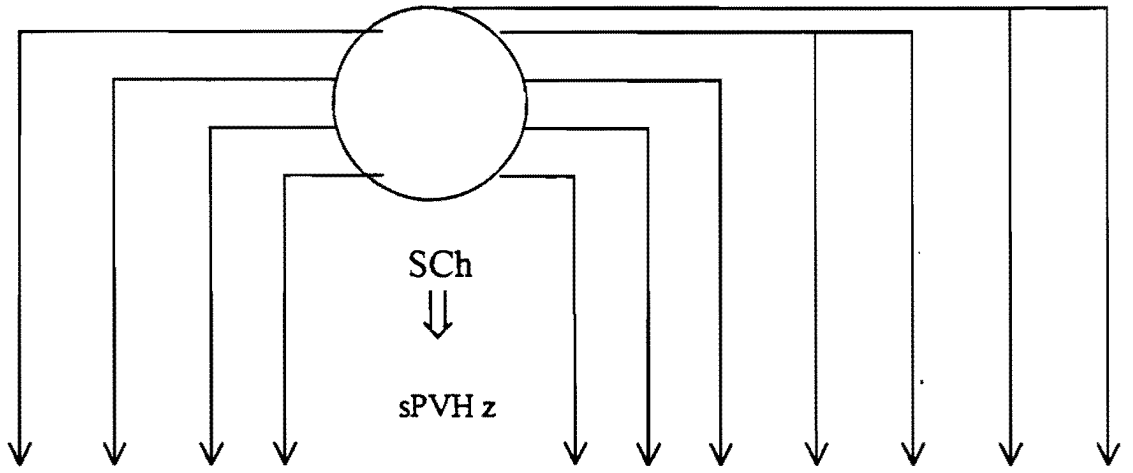
The process of establishing the efferent connections was a complex task – considering the small size of the SCN and its close relationship with major neuronal tracts. With the use of special anterograde tracing techniques ( e.g. titrating aminoacids, phaseolus vulgaris leucoagglutin (PHA-Z), degeneration studies, immunohistochemical studies and electrophysiological

studies) it was concluded that the projection pattern of the SCN is predominantly ipsilateral. It consists mainly of 6 anatomical components that project to intra- and extrahypothalamic areas. See Figure 2 (16).

Vasopressin (VP) is secreted by the SCN in a circadian nature. VP is the only known gene product to be secreted by the SCN in this manner. The systemic action of VP (antidiuretic effect on kidney and vasoactive effects on arterioles) is better understood than its role in the SCN.

The significance of the above is that the VP mRNA peptide's rhythm in the SCN and cerebrospinal fluid can be seen as a model for circadian regulation in a complex mammalian system. It is speculated that the rhythm of VP secretion by the SCN affects other areas via direct SCN efferents - VP neurons within the SCN terminate in the SCN itself, the subparaventicular zone of the hypothalamus and in the paraventricular nucleus of the hypothalamus. VP stimulates corticotrophin-releasing hormone (CRH) and it is possible that SCN VP may , via stimulation of hypothalamic CRH regulate the hypothalamic-pituitary-adrenal axis (17).

The excitatory neurotransmitter glutamate seems to be a major component in the RHT for regulating entrainment with the light/dark cycle. The GHT




| BST LS PVT /PT IGL | PVH POA RCh VMH DMH PHA PAG |
|---|---|

EXTRA HYPOTHALAMIC HYPOTHALAMIC

SCh = Suprachiasmatic nucleus BST = bed nuclei of stria terminalis
LS = Lateral septal nucleus
PVT/PT = paraventricular nucleus of thalamus
IGL = intergeniculate leaflet
PVH = paraventricular nucleus of hypothalamus
POA = preoptic area nuclei RCh = retrochiasmatic area
VMH = ventromedical nucleus of hypothalamus
DMH = dorsomedial nucleus of hypothalamus
PHA = posterior hypothalamic area PAG = periaqueductal gray
SPVHz = subparaventricular zone. Contains approximately ¾ of all SCN – efferents. It is the major terminal field for SCN efferents.



Figure 2 : Efferent SCN projections. (16)

plays some role, with neuropeptide Y as the putative neurotransmitter, in circadian rhythm entrainment, but at present there is no evidence that the GHT is essential for this purpose.

Studies to elucidate the role of serotonin ( from the midbrain raphe ) in the SCN points towards a possible role for serotonin in influencing either the perceived intensity of photic input or the photic responsiveness of the SCN to environmental lighting (18).

The SCN's subdivisions contain different neurotransmitters. The dorsomedial division contains arginine vasopressin (AVP) and the ventrolateral division vasoactive intestinal peptide (VIP ). GABA-ergic neurons are found in all these subdivisions. VIP , peptidine histidine isoleucine (PHI ) and gastrin releasing peptide (GRP ) together appear to play an important role in the SCN to control circadian rhythms.
The exact mechanism of how neurochemical signals enforce circadian rhythms is obscure (18).

Neurotransmitter and receptor binding (first messenger ) cause a change in second messenger levels that can lead to the induction of the transcription of immediate early genes (IEG) c-fos and jun (third messenger).The consequent translation of Fos and Jun proteins can increase transcription of

DNA (via a Fos-Jun dimer complex that binds to the DNA regulatory element, AP- 1 site) to increase the production of a particular protein.

Amongst the stimuli or conditions that are known to activate c-fos is light stimulation. It appears that there is a relative specific production of c-fos in the SCN. The internal SCN clock can be phase advanced; i.e. reset to an earlier time by light stimulation just before the expected onset of environmental light. IEG is believed to affect genes that regulate the circadian pacemaker (19 ).

Two genes have been identified that have the sole function of controlling rhythms - the period ("per") gene and the timeless ("tim") gene. Evidence is starting to suggest that the protein products of the per and tim genes - PER and TIM respectively - move between the cytoplasm and the nucleus of cells, regulating not only the expression of themselves, but also of other target genes. The messenger RNA encoding PER and TIM as a result of the process follows a circadian rhythm.

Both the "per" gene and "tim" gene are transcribed during the day. TIM-protein is however, degraded by a light-induced process and the day-time level of TIM-protein thus remains low because of this. In order for the

proteins to function PER has to bind to TIM to form a PER-TIM dimer complex. This, however, occurs only after sunset when TIM protein levels rise. The complex then becomes functional and enters the nucleus where it inhibits the transcription of its own genes as well as other target genes ( yet unidentified ). By morning PER and TIM levels have dropped and no longer inhibit transcription.

Recently a semidominant autosomal mutation named "clock" has been discovered. Mammalian genes related to clock and implicated in circadian rhythm control have been identified. The clock gene appears to regulate the circadian period and the persistence of circadian rhythmicity. Mice, that are homogenous for the clock mutation, show very long circadian periods with complete loss of circadian rhythmicity in constant darkness ( 19)(20)(21)(22)(23)(24).



2.2.2 The concept of interacting oscillators

In the previous section the SCN - pacemaker ( oscillator "y" ) was described. There is, however, evidence that a second or "x" oscillator exists, presumably outside the SCN. This second oscillator is involved in the regulation of body temperature.

When the SCN (or "y" oscillator) is destroyed, body temperature rhythm

will persist. These two oscillators are internally synchronized. Periodic zeitgebers are suspected to affect only oscillator "y". The oscillators affect each other - the effect of "x" on "y" is about four times greater than "y" on "x". These two oscillators can become desynchronized. Under these circumstances other physiological rhythms will either follow the sleep-wake ("y" oscillator) or temperature ("x" oscillator) pattern (25).

2.2.3 The. Pineal Gland

The pineal gland, once called "the seat of the soul"(Descartes), is a diencephalic structure, and part of the epithalamus(14). The pineal gland is attached to the posterior part of the roof of the third ventricle, and is also part of the circumventricular system. The human pineal gland is 5 x 7 mm in size and weighs 100 - 150 mg (26). See Figure 3 for the anatomical relationships of the pineal gland (27). Its relationship to other structures in the photoneuronendocrine system is shown in Figure 4 (28 ).

Melatonin synthesis and metabolism are described in detail in the literature (14) (29) and only an overview is shown in Figures 5 and 6 (29). The synthesis of melatonin from tryptophan is under sympathetic noradrenergic control with N-acetyltransferone (NAT) as the rate limiting enzyme. NAT's activity can increase up to a hundredfold at night. Melatonin undergoes a

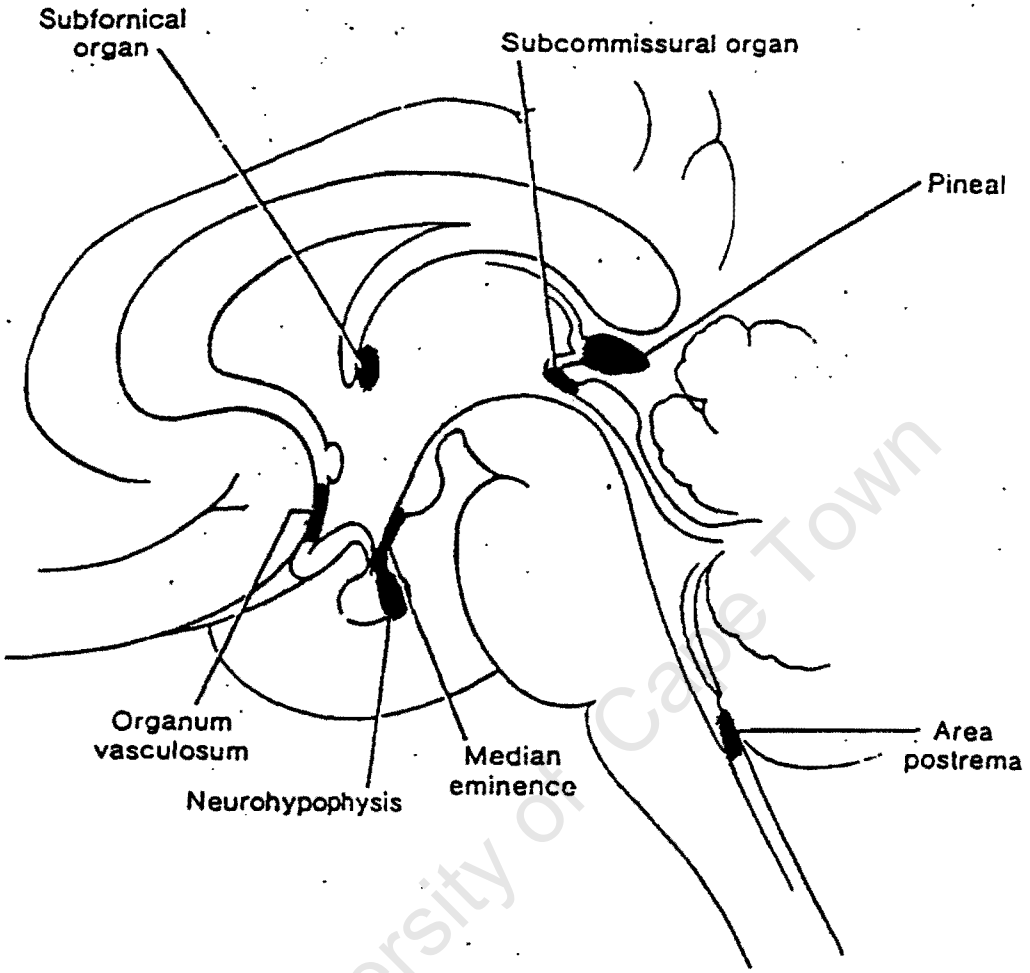





Figure 3 : The pineal gland. A circumventricular organ – its anatomical relationships. (27)

- The pineal organ is capable of humoral(hormonal) and neural types of signals; the corresponding target areas are only partly known.

**SUPRACHIASMATIC NUCLEUS**

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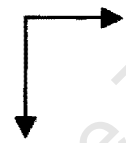
**PINEAL PHOTORECEPTORS**



**EXTRARETINAL HYPOTHALAMIC PHOTORECEPTORS**


**RETINOHYPOTHALAMIC PATHWAYS**

The retinohypothalamic pathway project to circumscribed hypothalamic areas (HTH), which may also be the target of signals originating in the deep hypothalamic (encephalic) photoreceptor. Both mechanisms appear to serve the control of adenohypophyseal (HYP) functions.


Figure 4 : The photoneuroendocrine system. Diagrammatic representation of the general concept of photoneuroendocrine systems.

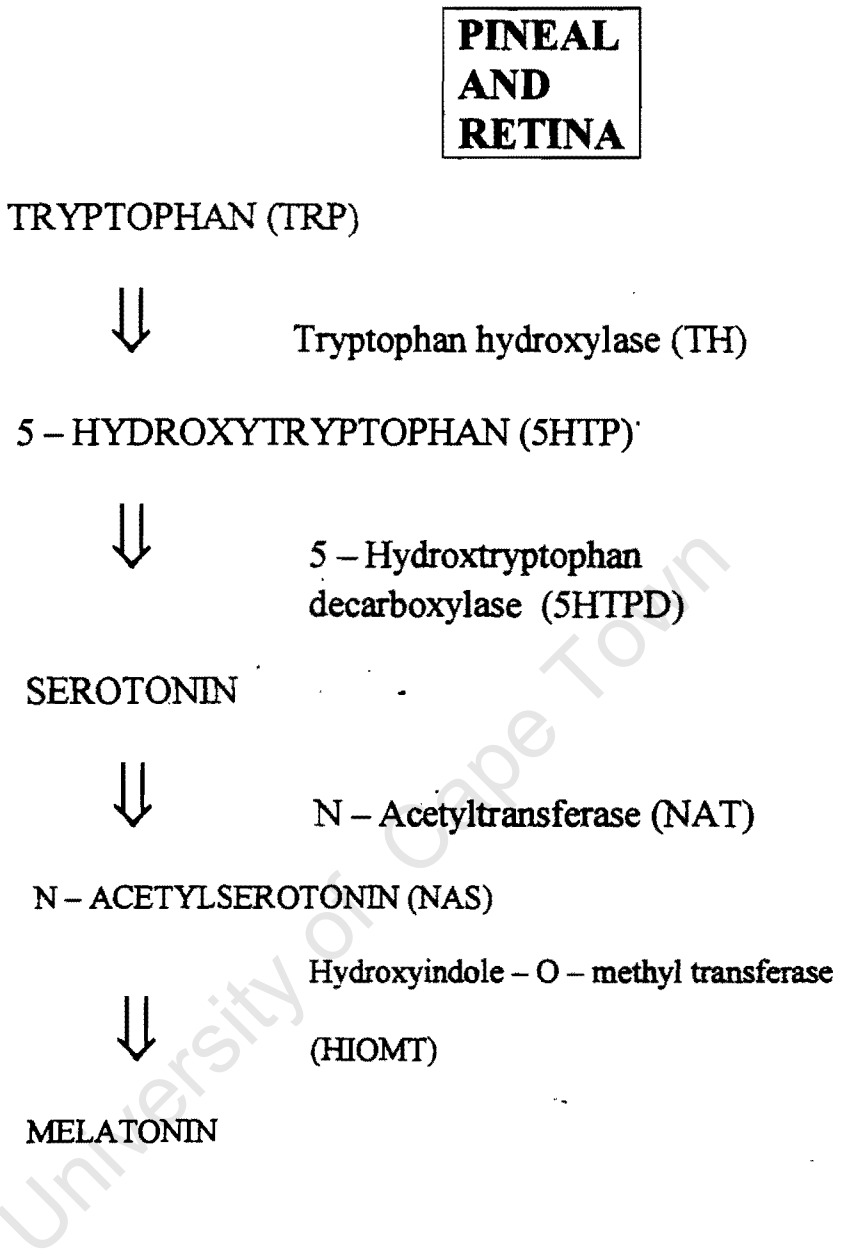





Figure 5 : Melatonin synthesis (29).

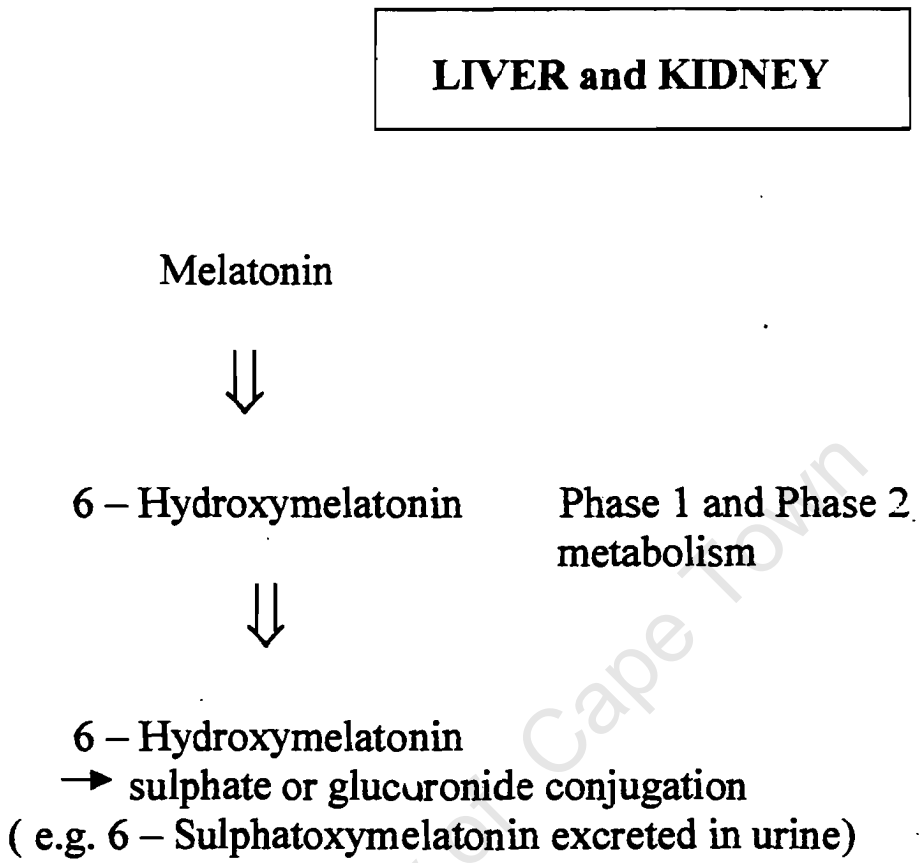





Figure 6 : The metabolism of Melatonin (29)

microsomal phase I and 2 reaction in the liver – hydroxylation followed by sulphate or glucoronide conjugation and is excreted through the kidneys (14)(29).

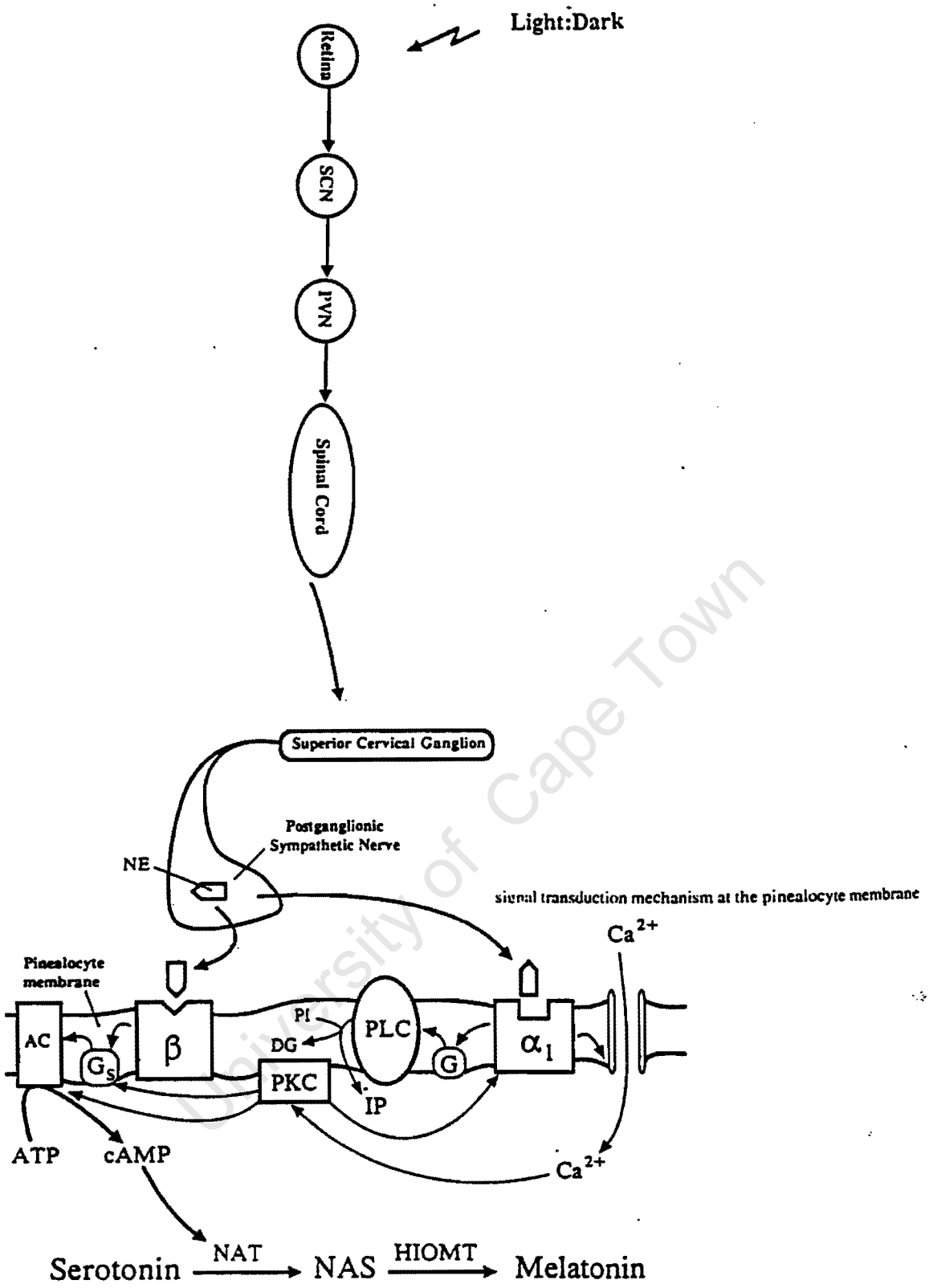
Figure 7 illustrates the probable pathways from the retina to the pineal gland by which pinealocytes are innervated by the noradrenergic system (29).

Melatonin has been shown to influence circadian rhythms. This is thought to be via high affinity melatonin receptors in the SCN. These melatonin receptors seem to have maximal high affinity binding for melatonin at the late onset period.

Melatonin has also been associated with the regulation of a variety of other physiological functions, e.g. activity levels, feeding, drinking, body temperature and the seasonal timing of reproduction and metabolism. It has been said that melatonin refines the events of life (30)(31)(32)(33).



An important aspect that is often overlooked is that the pineal gland also contains a multitude of other neurotransmitters and receptors for amino acids, biogenic amines and peptides. Of these the noradrenergic system is probably the best studied, but the exact function of other neurotransmitter systems, e.g. the gaba-ergic, dopaminergic, glutaminergic, muscarinergic and substance P is not understood as yet. There is evidence that melatonin's




(AC) adenylate cyclase; (DG) diacylglycerol; (G) guanine nucleotide binding protein (G-protein); ($G_s$) stimulatory G-protein; (HIOMT) hydroxyindole-*O*-methyltransferase; (IP) inositol phosphate; (NAS) *N*-acetylserotonin; (NAT) *N*-acetyltransferase; (NE) norepinephrine; (PI) phosphoditylinositol; (PKC) protein kinase C; (PLC) phospholipase C; (PVN) paraventricular nuclei; (SCN) suprachiasmatic nuclei; ($\alpha_1$) $\alpha_1$-adrenergic receptor; (β) β-adrenergic receptor.

Figure 7 : Proposed neural pathways between the eye and the pineal gland. (29)

interaction with dopamine may play a role in maintaining the function of the extrapyramidal motor system (33)(34)(35). A better understanding of these issues will have a positive impact on clinical psychiatric practice.

The serotonin concentration of the pineal gland seems to enjoy special protection. The pineal gland has a serotonin concentration a hundred times that of the brain. During serotonin depletion studies the brain's serotonin level will start to decrease first, thereby sparing the pineal gland initially, before the pineal gland's serotonin level will start to diminish(36).

There is an inverse relationship between serotonin and melatonin levels in the pineal gland : the melatonin level is highest during night time ( serotonin levels lowest) and the serotonin level is highest during day time (melatonin levels lowest) (26).

By convention, light pulses are used to investigate the control of circadian rhythms. A phase response curve (PRC) is a protocol that was developed from observations on activity-rest-cycles. During these experiments animals are kept in constant darkness to ensure free-running rhythms (i.e. not entrained by zeitgebers). The period (tau) of the free-running cycle is divided into 24 circadian hours (tau/24 i.e. using circadian time as a descriptor). In rodents the daily onset of nocturnal wheel running activity is

the phase reference point for the rhythm and is designated CT 12 (circadian 12 ) and indicates the start of the subjective night. Please see Chapter 6 for an explanation of terminology.

The phase reference point for melatonin's PRC is either the onset of the rise in plasma melatonin in the evening, or the calculated peak time, or the morning and evening onset and offset of N-acetyltransference ( the rate limiting enzyme in melatonin synthesis). A single light pulse can shift the phase of a free-running rhythm. The direction and magnitude of the shift will depend on the circadian time at which the light pulse is administered.

Phase advances (i.e. a shift forward) are obtained by administering light in the middle to late subjective night and early subjective day. Phase delays (i.e. shift backward) are obtained by light being administered in the late subjective day and early subjective night. The subjective day represents a dead zone during which no shifts can be induced. The PRC thus represents the direction and magnitude of the shifts obtained in response to light pulses (26).

# CHAPTER 3 :

# CLINICAL RELEVANCE TO PSYCHIATRIC DISORDERS

## 3.1. Introduction

Reflecting on the extrapolation of experimental animal data to the generation of hypotheses on the neurobiology of psychiatric disorders, researchers in psychiatry were faced with the problem that diseased tissue (brain) could not readily be collected from living patients suffering from psychiatric disorders. The study of post mortem tissue in psychiatric research has thus become more common(37). The assumption is that post mortem studies can act as a bridge between animal experiments and clinical studies(38).

The training of psychiatrists in South Africa aims to produce a competent general specialist psychiatrist (39). Although a thorough grounding in neural sciences is obtained, few psychiatrists will follow a career path that would equip them with the high technology skills that are necessary to conduct research as described in the above paragraph.

I would, however, like to propose that chronobiology offers the general specialist psychiatrist an opportunity to contribute to our knowledge base in psychiatry. By presenting clinical examples of the importance of biological rhythms in mental illness, it is hoped that the concept of chronobiology in

psychiatry will be promoted.

3.2. Seasonal Affective Disorder

For over 2000 years the effect of seasonal changes on the course of affective (mood) disorders have been noted. Two opposite seasonal influences on mood disorders were observed - the one begins in fall and peaks in winter, while the other starts in spring and peaks in summer. The variation of the environment at different latitudes and the supposed effect of this on mood contributed to the prescription of climatotherapy, i.e. traveling to a different climate and latitude as treatment of mood disorders.

From ancient times the role of darkness in depression was considered. Hippocrates wrote about" black humor" and its darkness that throws a shadow over the area of thought, comparing it with environmental darkness that makes people fearful (40).

Rosenthal et al published a description of seasonal affective disorder(SAD) and their preliminary results with light therapy in 1984. They concluded that SAD is a subgroup of the mood disorders, but also that more research was needed to validate SAD as a distinct syndrome ( e.g. studies on demographics, family history, laboratory studies, outcome and treatment response). They commented on the fact that the main features of SAD -

hypersomnia, overeating, weight gain and carbohydrate craving - are not represented on the Hamilton Rating Scale and that fatigability is also given a light weight. The severity of the depression can thus be underestimated (41). See Figure 8 for a working definition of SAD.

The two opposite seasonal depressions also received attention. It was reported that these two seasonal types of depression have opposite types of neuro vegetative symptoms. Winter depression tends to have more atypical features namely increased appetite, carbohydrate craving, weight gain and hypersomnia. Summer depression is more likely to present with decreased sleep and appetite (42)(43)(44).

As with most psychiatric disorders, SAD is a syndrome, i.e. described by symptoms and signs, clustered together to form a diagnosable entity. Various theories regarding the etiology of this syndrome have been put forward (45).

The dopaminergic system has been implicated by suggestions that a basic behavioral system (the basic facilation system - BFS) which mobilizes an organism to engage with its environment under appropriate stimulus conditions is thought to be activated by inherently rewarding stimuli. The BFS is supposedly composed of two major components:

Suggested working definition of SAD by Rosenthal et al (41)

1. History of major affective mood disorder according to the Research Diagnostic Criteria.

2. At least two consecutive years in which depression developed during Fall or Winter and went in remission during the following Spring or Summer.

3. Absence of any other Axis 1 Psychiatric Disorder.

4. Absence of clear psychosocial variables that change seasonally that could explain seasonal changes in mood.

Figure 8 : The definition of SAD.

# LA - initiation of locomotor activity

# Incentive - reward motivation.

It seems that BFS activity - and thus behavioral engagement - is associated with a positive mood. This leads to an organism obtaining rewards.

The BFS suggests a motor affective model for the level of engagement by an organism with its environment - if engagement is low it would signal the absence of a positive mood. Dopamine has been shown to be the primary neurotransmitter in the initiation of LA and is also involved in the incentive type of reward that activates goal acquisition (45).

SAD appears to have extreme states of engagement with the seasonal changes - which raised the possibility of seasonal alternations in BFS functions (45). By investigating melatonin secretion in constant dim light in winter and summer it was noted that the duration of the nocturnal period of higher melatonin secretion was longer in winter than in summer in patients suffering from SAD.

This difference is seen as indicative of patients with SAD having a biological signal that the season is changing - this signal is presumed to be the same as that used by mammals to adapt behavior to seasonal change.

Healthy volunteers did not display evidence of such a signal. The effect of living in a modern urban environment - not exposed to sunlight at daytime / exposed to artificial light at night time - on the ability of the pacemaker to detect the natural photoperiod has not been clarified as yet (46)(47)(43).

The possibility that patients suffering from SAD might have deficient retinal photoreceptors also needs further investigation(49).

Terman suggested that it may be useful to chronotype patients/controls (i.e. larks vs. owls) using a scale of morningness and eveningness. See Figure 9 and Figure 10 (50)(51). Serotonin is also believed to play a role in the etiology of SAD. Fenfluramine ( serotonin releasing and re-uptake inhibitor) yielded positive results in the treatment of SAD in a small preliminary study (52). 5- Hydroxytryptophan ( 5-HT) administered orally to patients/controls caused an significant increase in cortisol levels, and a decrease in prolactin levels in both the patient and the control groups. No differences were noted in the melatonin level, growth hormone(GH) level, blood pressure or pulse rate between patient and control groups. These findings argue against the importance of melatonin secretion on SAD. However, the use of a more selective serotonergic agonist is advocated when functional serotonergic activity in patients with SAD is investigated, because 5-HT can also

Figure 9:

The Automated Morningness-Eveningness Questionnaire (51)

There will be 19 questions about your daily sleep-wake habits and the times of day you prefer certain activities. Answering should take only about 5-10 minutes. As soon as you finish, you will receive personalized feedback.

For each question, select the answer choice that best describes you. Base your judgments on how you have felt in recent weeks.

*Use the **next** button at the bottom of the screen to move to the next question.*
*If you want, you can also use the **previous** button to review earlier questions and change your answers.*

previous next

| | | |
|---|---|---|
| 1<br>(18 questions left) | *Approximately* what time would you get up if you were entirely free to plan your day?<br><br>*(You may want to use your browser's zoom function to maximize the size of the question text on your screen.)* | --Select one of the following--<br>1) 5:00-6:30 a.m.<br>2) 6:30-7:45 a.m.<br>3) 7:45-9:45 a.m.<br>4) 9:45-11:00 a.m.<br>5) 11:00 a.m.-12:00 noon<br>6) 12:00 noon-5:00 a.m. |

previous next

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| 2<br>(17 questions left) | *Approximately* what time would you go to bed if you were entirely free to plan your evening? | --Select one of the following--<br>1) 8:00-9:00 p.m.<br>2) 9:00-10:15 p.m.<br>3) 10:15 p.m.-12:30 a.m.<br>4) 12:30-1:45 a.m.<br>5) 1:45-3:00 a.m.<br>6) 3:00 a.m.-8:00 p.m. |

previous next

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| 3<br>(16 questions left) | If you usually have to get up at a specific time in the morning, how much do you depend on an alarm clock? | --Select one of the following--<br>1) Not at all<br>2) Slightly<br>3) Somewhat<br>4) Very much |

previous next

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| 4<br>(15 questions left) | How easy do you find it to get up in the morning (when you are not awakened unexpectedly)? | --Select one of the following--<br>1) Very difficult<br>2) Somewhat difficult<br>3) Fairly easy<br>4) Very easy |

previous next

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| 5<br>(14 questions left) | How alert do you feel during the first half hour after you wake up in the morning? | --Select one of the following--<br>1) Not at all alert<br>2) Slightly alert<br>3) Fairly alert<br>4) Very alert |

previous next

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| 6<br><br>(13 questions left) | How hungry do you feel during the first half hour after you wake up? | --Select one of the following--<br>1) Not at all hungry<br>2) Slightly hungry<br>3) Fairly hungry<br>4) Very hungry |

previous next

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| 7<br><br>(12 questions left) | During the first half hour after you wake up in the morning, how do you feel? | --Select one of the following--<br>1) Very tired<br>2) Fairly tired<br>3) Fairly refreshed<br>4) Very refreshed |

previous next

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| 8<br><br>**(11 questions left)** | If you had no commitments the next day, what time would you go to bed compared to your usual bedtime? | Please answer this question<br>--Select one of the following--<br>1) Seldom or never later<br>2) Less than 1 hour later<br>3) 1-2 hours later<br>4) More-than 2 hours later |

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| 9<br><br>(10 questions left) | You have decided to do physical exercise. A friend suggests that you do this for one hour twice a week, and the best time for him is between 7-8 a.m. Bearing in mind nothing but your own internal "clock," how do you think you would perform? | --Select one of the following--<br>1) Would be in good form<br>2) Would be in reasonable form<br>3) Would find it difficult<br>4) Would find it very difficult |

previous next

| | | |
|---|---|---|
| 10<br><br>(9 questions left) | At *approximately* what time in the evening do you feel tired, and, as a result, in need of sleep? | --Select one of the following--<br>1) 8-9 p.m.<br>2) 9-10:15 p.m.<br>3) 10:15 p.m.-12:45 a.m.<br>4) 12:45-2:00 a.m.<br>5) 2-3 a.m. |

previous next

| | | |
|---|---|---|
| 11<br><br>(8 questions left) | You want to be at your peak performance for a test that you know is going to be mentally exhausting and will last two hours. You are entirely free to plan your day. Considering only your internal "clock," which one of the four testing times would you choose? | --Select one of the following--<br>1) 8-10 a.m.<br>2) 11 a.m.-1 p.m.<br>3) 3-5 p.m.<br>4) 7-9 p.m. |

previous next

| | | |
|---|---|---|
| 12<br><br>(7 questions left) | If you got into bed at 11 p.m., how tired would you be? | --Select one of the following--<br>1) Not at all tired<br>2) A little tired<br>3) Fairly tired<br>4) Very tired |

previous next

| | | |
|---|---|---|
| 13<br><br>(6 questions left) | For some reason you have gone to bed several hours later than usual, but there is no need to get up at any particular time the next morning. Which one of the following are you most likely to do? | --Select one of the following--<br>1) Will wake up at usual time, but will not fall back asleep<br>2) Will wake up at usual time and will doze thereafter<br>3) Will wake up at usual time, but will fall asleep again<br>4) Will not wake up until later than usual |

previous next

| | | |
|---|---|---|
| 14<br><br>(5 questions left) | One night you have to remain awake between 4-6 a.m. in order to carry out a night watch. You have no time commitments the next day. Which one of the alternatives would suit you best? | Please answer this question<br>--Select one of the following--<br>1) Would not go to bed until the watch was over<br>2) Would take a nap before and sleep after<br>3) Would take a good sleep before and nap after<br>4) Would sleep only before the watch |

previous next

| | | |
|---|---|---|
| 15<br><br>(4 questions left) | You have to do two hours of hard physical work. You are entirely free to plan your day. Considering only your internal "clock," which one of the following times would you choose? | --Select one of the following--<br>1) 8-10 a.m.<br>2) 11 a.m.-1 p.m.<br>3) 3-5 p.m.<br>4) 7-9 p.m. |

previous next

| | | |
|---|---|---|
| 16<br><br>(3 questions left) | You have decided to do physical exercise. A friend suggests that you do this for one hour twice a week. The best time for her is between 10-11 p.m. Bearing in mind only your own internal "clock," how well do think you would perform? | --Select one of the following--<br>1) Would be in good form<br>2) Would be in reasonable form<br>3) Would find it difficult<br>4) Would find it very difficult |

previous next

| | | |
|---|---|---|
| 17<br><br>(2 questions left) | Suppose you can choose your own work hours. Assume that you work a five-hour day (including breaks), your job is interesting and you are paid based on your performance. At *approximately* what time would you choose to begin? | --Select one of the following--<br>1) 5 hours starting between 4 a.m. and 8 a.m.<br>2) 5 hours starting between 8 a.m. and 9 a.m.<br>3) 5 hours starting between 9 a.m. and 2 p.m.<br>4) 5 hours starting between 2 p.m. and 5 p.m.<br>5) 5 hours starting between 5 p.m. and 4 a.m. |

previous next

| | | |
|---|---|---|
| 18<br><br>(1 question left) | At *approximately* what time of day do you usually feel your best? | --Select one of the following--<br>1) 5-8 a.m.<br>2) 8-10 a.m.<br>3) 10 a.m-5 p.m.<br>4) 5-10 p.m.<br>5) 10 pm-5 a.m. |

previous next

| | | |
|---|---|---|
| 19<br><br>(last question!) | One hears about "morning types" and "evening types." Which one of these types do you consider yourself to be? | --Select one of the following--<br>1) Definitely a morning type<br>2) Rather more a morning type than an evening type<br>3) Rather more an evening type than a morning type<br>4) Definitely an evening type |

previous next

| OWLS | LARKS |
| --- | --- |
| -- Melatonin onset later than 10 pm | -- Melatonin onset before 5pm |
| -- Remission of depression in spring | -- Remission of depression in spring |
| -- Greater spring time phase advance ( d = 153 ) | -- Seize effect for phase advance in spring negligible ( d = 0,22 ) |
| -- Benefit from morning light therapy in winter | -- Benefit from morning light therapy in winter, but need treatment much earlier |

Figure 10 : Owls vs Larks ( 50)

displace dopamine from central nervous stores, thus increasing dopamine activity that can account for the significant drop in prolactin levels (53).

The area of neuroendocrine rhythms has been investigated for some time with the following conclusions :

- ACTH amplitude and cortisol secretion are elevated in major depressive episode,
- the onset of HPA activation is phase advanced in patients with hypercortisolaemia, but that HPA activation is equally phase delayed,
- that the amplitude of melatonin rhythms is reduced in depression is ambiguous,
- the overall neuroendocrine rhythms function fairly well in depressed patients although disruption of GH, prolactin and TSH secretion have been reported,
- diurnal variation in mood may be related to the endogenous rhythm of cortisol. (54)



Other hypotheses regarding the pathophysiology of SAD include the photonhypothesis ( not receiving a sufficient quota of light to sustain an euthymic state), the amplitude hypothesis ( endogenous circadian amplitudes of temperature, melatonin and heart rate can be suppressed or enhanced by timing the exposure to light) and a complex model involving the eye. See Table l(55 ) for a summary of the hormonal profiles of patients suffering from SAD (55).

| | SUBSTANCE | CHANGE RELATIVE TO NORMALS |
|---|---|---|
| Plasma | Growth hormone | Delayed nocturnal peak |
| | Cortisol | Unchanged |
| | Prolactin | Reduced |
| CSF | Homovanillic acid | Unchanged |
| | MHPG | Unchanged |
| | 5 – HIAA | Unchanged |
| Challenges | m-CPP | Increased activation and euphoria in Winter; increased cortisol and prolactin |
| | DST | Unchanged |
| | CRH | ACTH response blunted |

Table 1 : Hormonal profiles of SAD. ( 55 )

Recent research showed that catecholamine depletion with alpha - methyl – para - tyrosine (AMPT) induced a relapse in patients with SAD (in summer remission ). These findings raise the possibility that AMPT- induced depressive relapse is a trait marker for SAD (56).

It is not clear what the influence of latitude is on SAD. The effects of genetic vulnerability, cultural and social factors and climate seem to be more important than that of latitude (57).

The Seasonal Pattern Assessment Questionnaire (SPAQ) is widely used to identify patients with a seasonal pattern of recurrent major depressive disorder (MDD)– this instrument was initially developed as a screening tool. It was , however, found that, although it is useful to obtain information regarding recent seasonal variation in MDD, it had a low test-retest reliability (58). The SPAQ was also not able to accurately discriminate between SAD and subsyndromal SAD (S-SAD). The SPAQ's sensitivity was found to be 94%, specificity 73% and positive predictive value 45%(59). See Figure 11 for a brief explanation of the SPAQ. The SPAQ's central feature is the six item Seasonality Scale Index (SSI) that measures seasonal variation in mood, appetite, weight, sleep, energy and socialising. A good internal consistency for these six items was reported (alpha 0,82)(60).

The following sections are covered in the SPAQ:

1. Demographics
2. Seasonal change in sleep, social activity, mood, weight, appetite And energy level
3. Months in which 5 indicators are at best or worst
4. Weather preference for specific types of days
5. Weight fluctuations over a year
6. Number of hours sleep in every 24-hour period during each of the seasons is recorded
7. Global rating scale (experience of severity of seasonal changes).



Figure 11 : Seven sections of The Seasonal Pattern Assessment Questionnaire (58) (59) (98).

Research shows that patients suffering from SAD frequently attend health care services, and that the illness is still under diagnosed and thus under treated (61)(62)(63).

3.3. Anxiety Disorders

Seasonal panic disorder has been described and may be a variant of SAD (64). Diurnal variation of particular symptoms - phobia and generalized anxiety – have been noted in subgroups of patients with panic disorder. The possibility of ultradian rhythms relating to various subtypes of anxiety symptoms needs further investigation (65).

The observation that patients with major depressive illness frequently have panic attacks has been extended to patients suffering from recurrent major depression. It is believed that up to 24% of patients with recurrent major depression have a state dependent panic disorder (66).

The circadian secretion of vasopressin in the SCN was described in Chapter 2. Although abnormalities of vasopressin, corticotrophic releasing factor and somatostatin have been described (66)(67)(68), a small study could not find a greater degree of seasonal variation in patients suffering from OCD. Light therapy also proved to be unsuccessful as treatment (69).

The SPAQ identified individuals with generalized anxiety and marked

seasonal changes(59).

3.4. Eating Disorders

Clinical evidence suggests that that the prevalence of eating disorders can be expected to increase - with female vulnerability the most common denominator. The fact that 80% of females were on a diet at the age of 13 years indicates the level of dissatisfaction that adolescent girls have with their body image (70) (71). Arguments are that some physiological events sustain eating disorders, e.g. gastric emptying is delayed in anorexic patients and that cholecystokinin (CCK) amongst others inhibits feeding and gastric emptying. It is also suggested that if the stomach can entrain its emptying rate according to the rate of food supply that this may be controlled by central and peripheral processes that can be neural or chemical in nature (72).



The circadian cycle was shown to influence postprandial lipid metabolism – triacylglicerol levels were higher after a meal taken at night time than during the day (73). This can be a significant risk factor for individuals with night eating syndrome. This syndrome consists of evening hyperphagia, insomnia and morning anorexia , and individuals consume 65% of their energy intake between 20h00 and 06h00. This circadian pattern of behavior is

accompanied by altered circadian neuroendocrine findings, i.e. continuation of the usual nocturnal rise in melatonin, peptin and plasma cortisol levels (74).

Binge eating and vomiting leads to an increase in metabolic rate - this is thought to be caused by the preabsorptive rebound of insulin, leading to the activation of the sympathetic nervous system and HPA axis , e.g. the thyroid axis (75). Hypothalamic dysfunction is common in individuals suffering from eating disorders (71).

There is an increasing amount of research data that show an overlap between seasonal affective disorder and bulimia nervosa. This has led to speculation that a common neurophysiological mechanism exists. Central serotonin metabolism in normal individuals has a seasonal rhythm with low serotonin levels during winter and higher levels in summer. Serotonergic tracts also run through the ventromedial hypothalamus(involved in the control of satiety) (76). Further evidence for the involvement of serotonin in eating disorders is derived from the effectiveness of serotonergic agents, e.g. fluoxetine and fenfluramine in the treatment of certain eating disorders (76) (77).

Preliminary studies have shown that phototherapy reduces the binge eating

and purge episodes in bulimic patients. Further studies on the circadian rhythm abnormalities in patients with bulimia nervosa are indicated as the chronopathology of bulimia nervosa is poorly understood (78).

3.5. Female Specific Mood Disorders

Premenstrual Dysphoric Disorder (PMDD), pregnancy, post-partum depression and menopause are female specific mood disorders in which disturbances in biological rhythms (chronopathology) are evident. Females become more susceptible to mood disorders than males after the onset of puberty. This is the time when the neuroendocrine reproductive axis regulates an ever-changing reproductive hormone profile. This is believed to affect the timing (phase) and amplitude of biological rhythms ( by disrupting the interaction of various components of the circadian system) in vulnerable individuals (79).



Gonadal steroids can modulate the GABA-ergic system during the menstrual cycle. Females suffering from PMDD have been shown to have a reduction in cortical GABA levels during the follicular phase. In contrast to healthy controls, patients with PMDD show an increase in cortical GABA levels from the follicular to the late-luteal phases (82). This information and the reported reduced sensitivity to benzodiazepines indicate that abnormalities

in GABA A receptor function feed back as GABA neural hypersensitivity to inhibitors of the GABA- ergic system(80) (81).

Numerous studies on PMDD discussed the possibility that various subgroups of PMDD exist. The endocrine abnormalities that occur in patients suffering from PMDD have been noted. Chronobiological abnormalities in patients suffering from PMDD are reflected by studies on circadian rhythmicity , e.g. sleep/activity temperature, melatonin, prolactin, cortisol and TSH (79). Manipulation of the serotonergic system seems a promising treatment modality. PMDD has diverse clinical features that needs further investigation. (82)(83)(84)(85).

The use of timed sleep deprivation in pregnant and post-partum patients needs further investigation and the augmenting effect of estroegen on antidepressant treatment in postmenopausal women can also reflect the loss of hormonal input into the maintenance of circadian physiology (79).



3.6.Disruption of social rhythms

Interpersonal relations and social demands, acting as social zeitgebers, may provide an important link between the neurobiological and psychosocial theories on the etiology of mental illness. See Figure 12 (36). The link between life events and depression is well established, but evidence for a

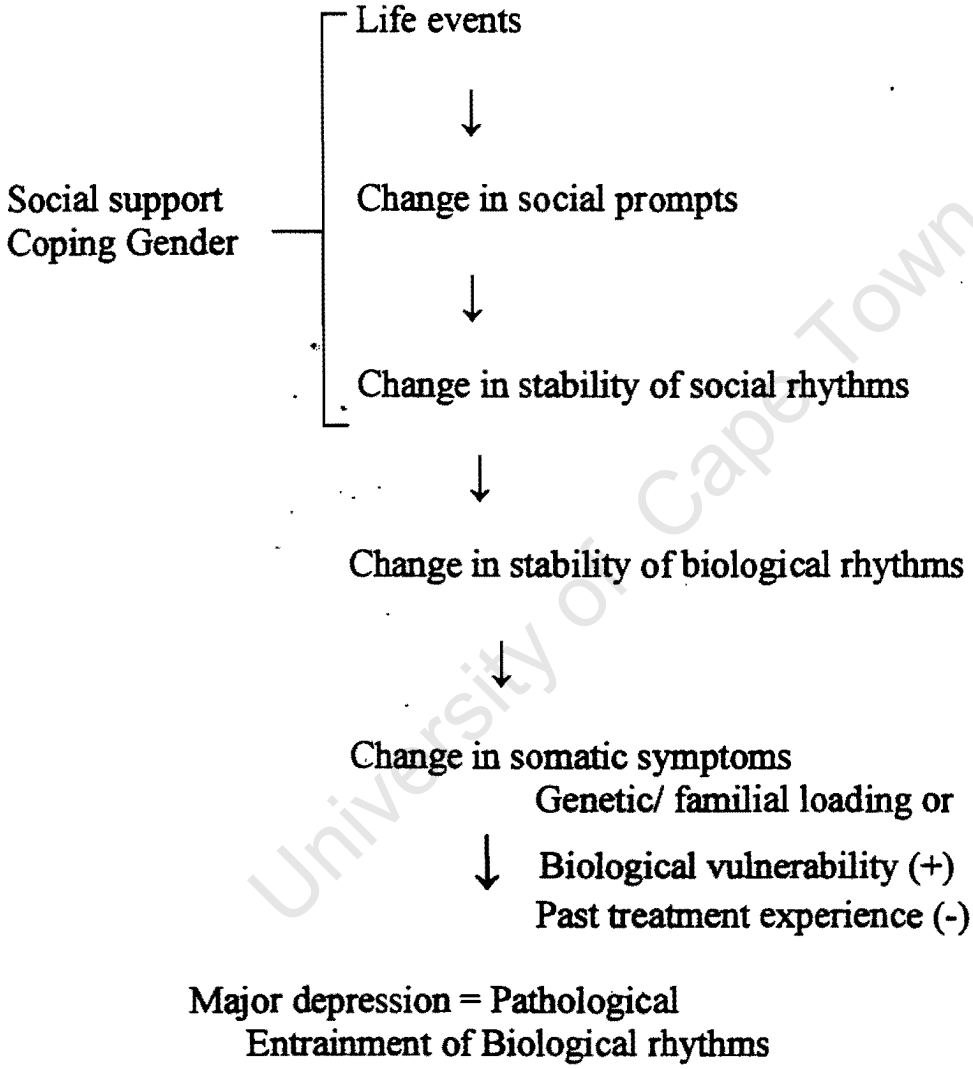



Figure 12 : Schema for social Zeitgeber theory. (86)

relationship between the onset of mania and the disruption of social rhythms is still ambiguous (87) (88). It is suspected that younger individuals have more event-related mania and it is speculated that life events may even bring manic presentations forward by as much as 20 years (89).

3.7. Seasonal variation in Suicide

Durkheim reported the seasonal nature of suicide as early as 1897 (90). In the Northern Hemisphere suicide peaks in spring/summer and has a through in autumn/winter. The suicide rate in Finland is amongst the highest in the world. The suicide rate of males in Finland has a unimodal peak in April to July, but females show a bimodal distribution in May and October. Elderly and non-violent suicides occur more often in autumn (91).

In the Southern Hemisphere spring starts in September, summer in December, autumn in March and winter in June. This seasonal pattern is thus the reverse from that in the Northern Hemisphere. It has been shown that suicide rates in South Africa also peak in spring/summer, irrespective or gender, race or ethnicity (92).

Alcoholism and/or substance abuse is the second leading contributing factor in 50% of all suicides. In comparing alcoholic patients with other diagnostic groups of suicide it was found that alcoholic patients showed a peak during

April - June. This may indicate that alcoholism may contribute to the spring peak in suicide (93). Recent results, however, suggest that the seasonal affect in England and Wales is diminishing and it is suggested that the seasonal variation in suicide may well disappear in the new millennium. The development of technology, enabling people to communicate more freely (cell phones, internet, telephone) is proposed to contribute to this trend (94).

3.8. Bipolar Mood Disorder

Although a seasonal trend in females with manic episodes was noted ( peak admission in England and Wales in August - September), it was not clear whether this was due to a seasonality of mania, or seasonality as a characteristic of the female sex (95).

Several reports since then, however, have documented disturbed circadian rhythms and a seasonal pattern in manic-depressive patients. It was shown that in patients with bipolar mood disorder, melatonin secretion was suppressed by light of 500 lux intensity, while control patients showed no suppression. This suggested that individuals with bipolar mood disorder might be supersensitive to light, which in turn has clinical implications (96). There is, however, still no conclusive evidence that bipolar patients have a seasonal pattern regarding their manic episodes (97) (98).

3.9. Psychosis

Periodicity in psychiatric disorders has been reported for many years and this is also true for psychotic disorders. Psychotic catatonia with episodes of stupor or excitement recur at predicted intervals and a subgroup of patients (hebephrenic) suffering from schizophrenia has been reported to exhibit behavioral abnormalities that oscillate in a rhythmic fashion. These observations suggest that if the biology of these rhythms could be unravelled, the rehabilitation potential of these subgroups of patients could be radically improved (99). Peak admission during the summer for psychotic patients have been reported since the nineteenth century. Subsequent reports indicate that only females suffering from schizophrenia have a summer peak of admissions(100).



3.10. Sleep Disorders

Disturbances in the sleep/wake cycle is a central issue in chronobiology (101)(102)(103). Sleep is vital to the homeostatic control of immune, autonomic nervous and neuroendocrine systems (104). Evidence points towards the hypothalamus and the hypocretin/orexin system as playing a more important role in regulating consciousness than was previously believed. The fact that gene expression is at a higher level during wakefulness and that it influences RNA and protein synthesis, metabolism,

use of sleep deprivation (105) (106) (107) (108).

Circadian Rhythms Sleep Disorder is one of the three Dyssomnias (i.e. disorders of sleep wakefulness in which patients either have difficulty initiating or maintaining sleep or sleep excessively) as described in the International Classification of Sleep Disorders. See Table 2 (109). Research on sleep continues to have clinical implications, e.g. development of rating scales such as the Columbia Jetlag Scale (see Table 3), and the review of current opinions and treatment strategies to name but two. It is commonly believed that 8 hours of sleep a night is required for good health, but a recent report indicate that people sleeping for 7 hours per night have the best survival rate. In addition, people sleeping less than 7 hours per night or for more than 8 hours had a significant higher mortality hazard. A significant increased mortality was found with the use of prescription sleeping tablets. (110) (111).



Mendelian circadian rhythm mutations can also occur. Individuals with Familial Advanced Sleep Phase Syndrome have an autosomal dominant circadian rhythm variant in which a missence mutation (changes a condon to code for a different aminoacid) in a clock component, hPER2, occurred (112).

Circadian Rhythms Sleep Disorders.

# Time zone change (Jetlag) Syndrome

# Shift Work Sleep Disorder

# Irregular Sleep/Wake Pattern

# Delayed Sleep Phase Syndrome

# Advanced Sleep Phase Syndrome

# Non – 24 – hour Sleep – wake Disorder

# Circadian Rhythm Sleep Disorder Not Otherwise Specified.



Table 2 : Circadian Rhythms Sleep Disorders (109).

## COLUMBIA JET LAG SCALE

- Today, how much have you been bothered (a) by
  Fatigue or tiring easily
  Trouble concentrating or thinking clearly
  Physical clumsiness
  Decreased daytime alertness
  Trouble with memory
  General feeling of weakness
  Light-headed, dizzy or other uncomfortable sensations in the head
  Lethargy or sluggish feeling
  Sleepiness during the day
- Overall, since you last got ready for night time sleep, how much were you bothered by symptoms of jet lag?(a)
- Approximate time napping during the day(b)
- Time of sleep onset last night
- Time of final awakening
- Times study capsules were taken

---

(a) Scale of 0-4 = not at all ; 1 = a little bit ; 2 = moderately; 3 = quite a bit ; 4= extremely.

(b) Scale of 0-4 = none ; 1 = 30 minutes ; 2 = 1 hour ; 3 = 2 hours ; 4 = 3+ hours.



Table 3 : Columbia Jet Lag Scale (110).

The prefrontal cortex, which, amongst others, is involved in the maintenance of wakefulness, the recruitment of cortical control, mediation, completion of tasks, planning, discrimination and maintenance of attention, seems to benefit in particular from sleep, especially human slow wave sleep (113).

A practical application of understanding circadian clues to sleep onset is illustrated by the fact that sleep follows thermoregulatory changes in the periphery. Vasodilatation in distal skin regions serves as a mechanism (via the onset of nocturnal melatonin secretion) to regulate sleep propensity. Cold feet and the inability to vasodilate may be one physiological cause of insomnia (ll4).



3.11. Neurological Disorders

It is becoming clear that the disruption of normal brain rhythms can lead to neurological diseases. It is hypothesized that abnormal 15 - 30Hz motor cortex oscillations gain access to the basal ganglia in Parkinsonism as a result of dopamine depletion(115).

Epilepsy is associated with abnormalities in the circadian rhythms of neuroendocrine functions. Primary generalized seizures occur mostly during the night. Dementia, cerebrovascular disease, movement disorders, neuromuscular disorders, multiple sclerosis and headaches all exhibit circadian rhythm components in their occurrence (116)(117)(118).

# CHAPTER 4
# SELECTED TREATMENT OPTIONS FOR SOME CHRONOPATHOLOGIES

The following is not intended to be a detailed account of any specific treatment, but will only serve as an overview of options that may be considered in the treatment of chronopathology related to psychiatric disorders. Further research into the application of these therapeutic options in the South African context is also needed.

## 4.1 Non – Pharmacological

### 4. 1. 1 Sleep Deprivation

The rapid antidepressant effect of sleep deprivation was revealed 3 decades ago. Due to the lack of financial support and the high rate of relapse patients experienced, interest in this form of treatment dwindled, with further research coming to a halt. Sleep deprivation was recently re-introduced as it is considered an important therapeutic option in the treatment of depressive syndromes. Efforts are being made to reduce relapse rate by concomitant drug therapy . The effect of multiple sleep deprivations is also under investigation (119) (120) (121). See Figure 13 for a proposed model of the antidepressant effect of sleep deprivation.

### 4.1.2 Light therapy

Daylight levels of illumination can change the phase of the endogenous circadian pacemaker. It also suppresses the production of melatonin. Bright

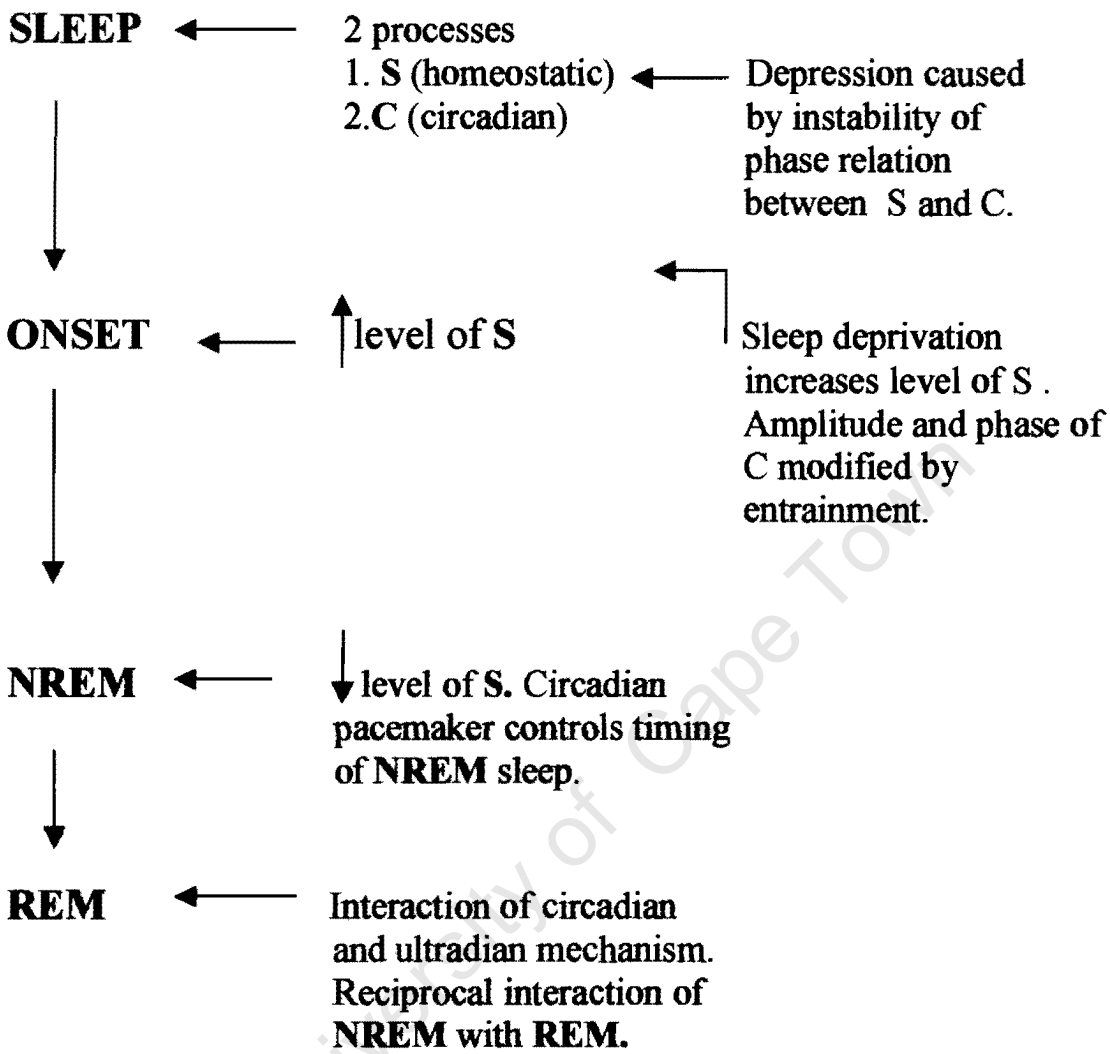





Figure 13: Sleep regulation and model of the effect of sleep deprivation in depression (119) (122).

light is thus a strong zeitgeber (123).

Rosenthal et al (40) and Wehr (41) published reports on the efficacy of light therapy in the treatment of mood disorders almost two decades ago. The effect of light on bulimia nervosa and mania is also under investigation (78 ) (96 ). A factor influencing research on light therapy is the difficulty of finding a suitable placebo for bright light (e.g. patients are able to distinguish between dim light and bright light) (124).

Other adjustments to social zeitgebers can also phase adjust the endogenous circadian pacemaker. General clinical applications or recommendations, however, remain problematic as there is an increased sensitivity to a mismatch between the phase of the endogenous circadian pacemaker (ECP) and the new social cues in the case of older people (123).



4.2. Pharmacological

Knowledge of the sensitivity/resistance cycle of an organism to enhance the desirable pharmacological effect or to reduce the side effect of drugs form the basis of chronotherapy/chronopharmacology. The study of chronopharmacology can be subdivided into

- chronopharmacodynamics
- chronopharmacokinetics

- chronopharmacotoxicology (125)(126).

The phenomenon that the efficacy of psychotropic drugs varies according to time of administration is true for mood stabilizers, benzodiazepines, anti-psychotics, anti-depressants and psychostimulants. Evidence points towards the role of rhythmicity in the neurotransmitter system ( neurotransmitters, receptors and second messengers) (126) (127).

The pharmacokinetics of lipophilic drugs can also be circadian-phase dependent. Peak drug concentration after oral dosing is usually higher after morning administration than with evening administration (128). Estimated hepatic blood flow is also believed to have a circadian pattern. This can be important when the pharmacokinetics of drugs with a hepatic blood flow-dependent clearance is interpreted (129) ( 130).

It is clear that the modulation of the neuroendocrine system by administering exogenous agonists/antagonists may prove to have significance. Melatonin has been investigated for its anxyolytic properties, mediating the effects of SSRI's in the treatment of OCD and improving sleep in jetlag and shift workers (131)(132)(133). Melatonin's role in phase resetting in delayed sleep phase syndrome has also been investigated (134). See Figure 14 (132 ) (135 ) for an example of how melatonin can assist in the treatment of jet lag

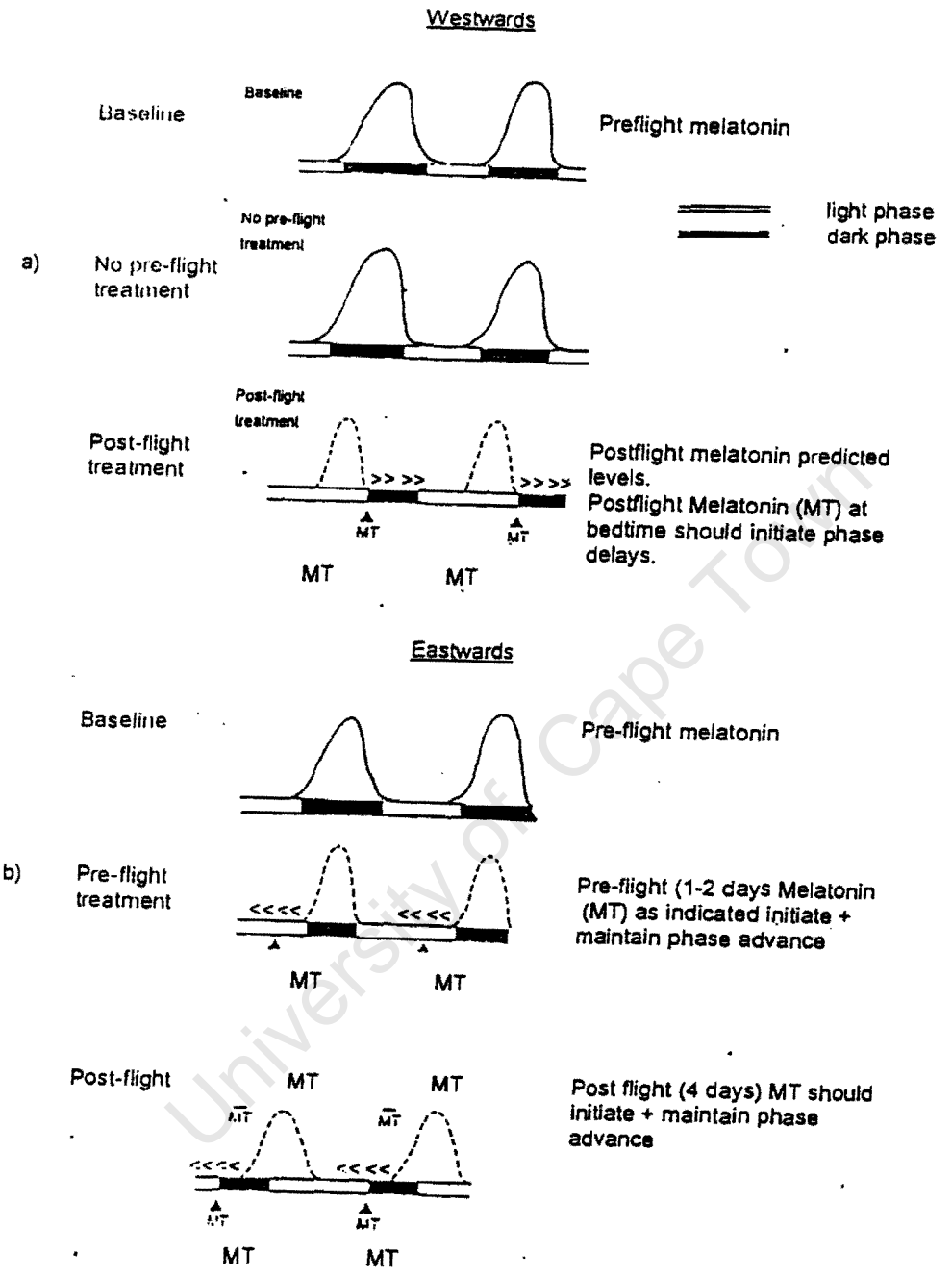





**Figure 14 : Example of how melatonin can assist in the treatment of jet lag (132) (135).**

and Figure 15 (132 ) (135 ) for the complex interaction of melatonin.

The role of lithium in sustaining the effect of total sleep deprivation and its ability to slow down circadian rhythms can also be of benefit to patients suffering from chronopathology. The two antidepressants clorgyline (MAOI) and imipramine (TCA) can also slow or dissociate circadian rest-activity rhythms ( 136) (137).

Unless psychiatrists in South Africa, however, have a clear understanding of chronobiology, the clinical skills to identify subgroups of patients suffering from chronopathology and a scientific protocol for the application of chronopharmacology, it is difficult to imagine that chronopharmacology will stand the scrutiny of evidence based medicine.

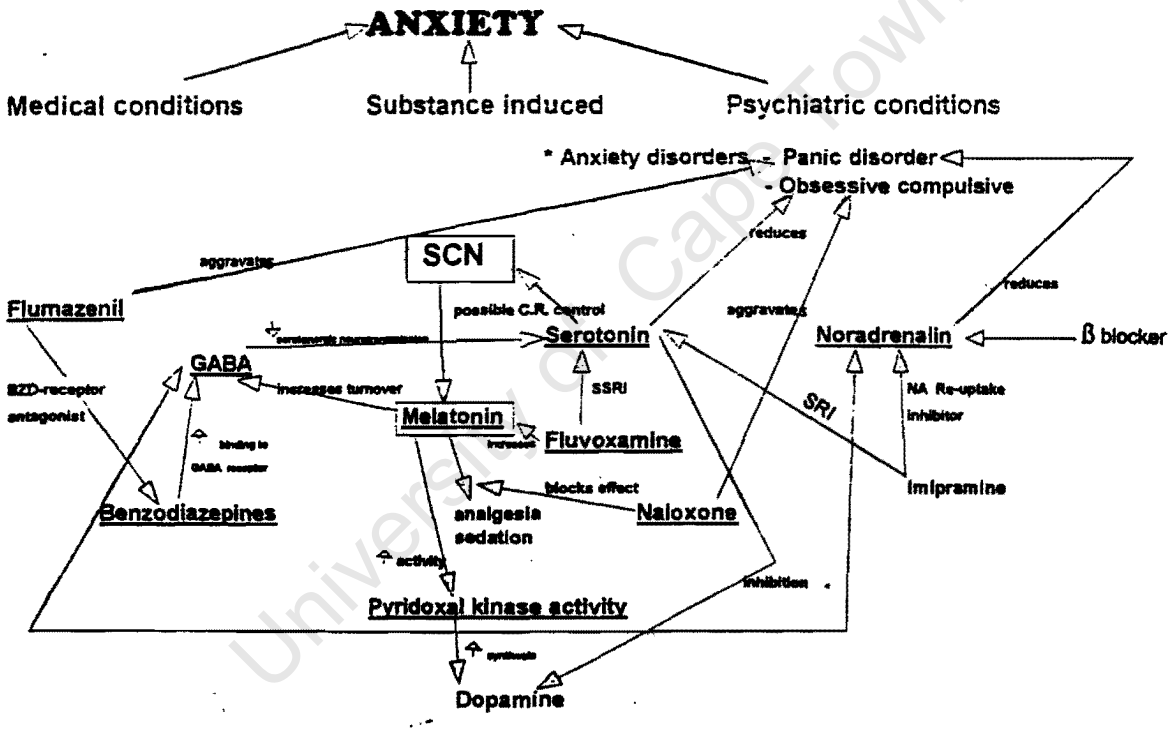



Figure 15 : Melatonin's interactions (132).

# CHAPTER 5
# DISCUSSION AND CONCLUSIONS

Research has shown that clinicians and the general public have very little knowledge of the temporal patterns in disease. There was even little difference in the accuracy of knowledge between the clinicians who claimed to have had exposure and knowledge of chronobiology and those who were unfamiliar with the concept of chronobiology. It was concluded that only once the concepts of chronobiology and chronotherapeutics are fully integrated in teaching programmes in medical schools will they be understood and correctly applied in clinical practice. In a survey in 1990 in the USA only an average of 1.16 hours throughout a 4-year programme per medical school was devoted to sleep and sleep disorders (138) (139).

My personal communication with various individuals who have a high profile in academic medicine and research in South Africa confirmed that there is no expertise in chronobiology relating to psychiatry in the country. Since an understanding of the chronopathology of disease, not only in psychiatry, but in medicine in general (asthma, myocardial infarction, peptic ulcers, hypertension, cancer) can lead to more cost-effective therapy and savings (money, person power, resources) , it is clear that the South African

psychiatrist can make an important contribution by promoting this important topic. I therefore propose a programme, which aims to achieve the following:

1.The introduction of a formal teaching programme for registrars in psychiatry on chronobiology. It is important that the curriculum is relevant to psychiatry as chronobiology is an extremely complex topic. This dissertation may serve as a basis for developing a curriculum as the various chapters will guide the presenter and the student through the process of integrating the relevant neuroanatomy, neurophysiology, chronopathology, pharmacology and other treatment principles. This will provide an overview of chronobiology relevant to psychiatry that is, according to my knowledge, not available in general psychiatric textbooks. Curriculum design for medical students is seen as a process that can change according to values and expectations and exists at three levels:

-What is planned for students?
-What is delivered to students?
-What the students experience? (140)

The candidate plans to present a course on chronobiology to candidates preparing for the FC Psych Part II at the University of Cape Town. This dissertation will form the basis of the content to be presented to the

candidates. Feedback from candidates can be used to refine the curriculum and adjust it to accommodate special needs and further developments.

2.Ultimately, this knowledge of chronobiology should be incorporated in psychiatric assessment and treatment. Specific questioning, such as the following, could alert the clinician to the possibility of underlying chronopathology:

- diurnal, nocturnal, weekly, monthly, seasonal, yearly variation of the presenting problem

- chronotype of the individual (owl or lark)

- medication or drugs of abuse and the time of ingestion that can influence biological rhythms (beta blockers, lithium, alcohol)

- social circumstances that lead to disrupted biological rhythms ( shift work, noise, small children). This is an important aspect of modern society that can have a tremendous detrimental impact on family life and the rearing of children.

- full assessment of neurovegetative features, e.g. night eating, overeating, carbohydrate craving, anorexia and assessment of the sleep pattern as phase advanced or phase delayed.

- fluctuation in cognitive function, e.g. deterioration of attention and concentration during the afternoon.

3. Journals on chronobiology should be more accessible. None of the main specialist journals in chronobiology are currently available in South Africa. For a list of these see references 101, 123, 125, 138, 143.

4. Research in chronobiology should be encouraged. The epidemiology, clinical features, diagnosis, chronopathology, treatment and prognosis of chronobiological disorders, specific to the South African population, offer opportunities for research. Research results may then be presented at national and international congresses to further stimulate discussion on the topic. Clinicians should furthermore be encouraged to obtain membership of the European Pineal and Biological Rhythms Society. Please see the Addendum for my contribution on the topic.

5. Health science planners should be encouraged to take an interest in the potential beneficial effects of light, exercise and sufficient sleep to improve productivity in the work place and quality of life in general (141).

6. Education of the general public is important to create an awareness of social zeitgebers that may impact on their quality of life.

Chronobiology offers an exciting opportunity for psychiatrists to make a contribution to our understanding of psychopathology, to collaborate with colleagues in other disciplines, to contribute to cost-effective treatment regimes and to reduce morbidity and mortality. This may be especially important in South Africa where there are many demands on the health care budget.

# CHAPTER 6
# TERMINOLOGY

## 6.1 SOME TERMS AND SYMBOLS USED IN CHRONOBIOLOGY

Biological rhythm parameters (see Table 4) cannot be expressed by a simple value, but must be established by an appropriate inferential statistical procedure (125). Assessment over a 24-hour period can be used to estimate a circadian rhythm by cosinor modeling (143). For a diagrammatical explanation of cosinor analysis see Figures 16 and 17 (144).

**Acrophase** Maximum of the function / the crest time of the cosine curve best fitting the data.

**Aschoff's Rule** The period of the free-running oscillation (r) lengthens on transfer from DD to LL or with an increase in light intensity for dark-active animals, but shortens for light-active animals.

**Circadian rhythm** An endogenous biological oscillation with a natural period ( r ) close to, but not necessarily equal to that of the solar day (24 hours).

**Circadian time (Ct)** Time scale, in hours or subdivisions of the circadian period, covering one full period of the oscillation (i.e. Ct 00 to Ct 24).

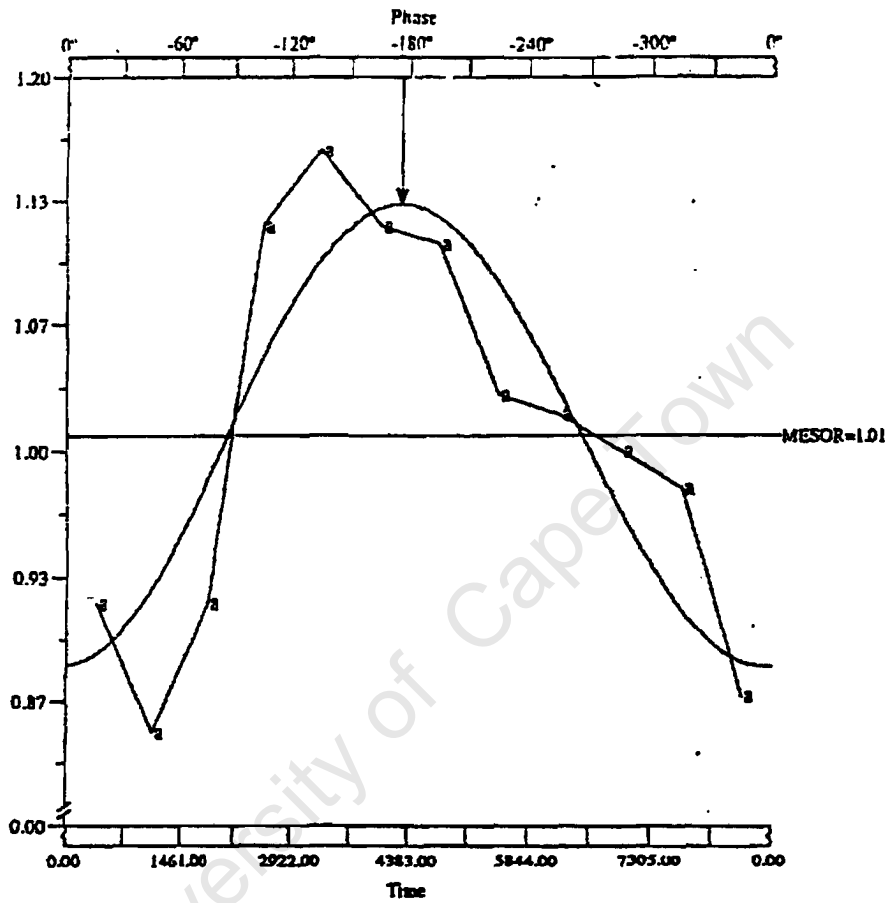
**Circatidal, circasyzygic, circalunar, circaannual rhythms** Endogenous biological oscillations with a natural period ( r ) close to the tidal cycle (12,4 hours), the spring tide to spring tide cycle (14,7 days), the lunar cycle (29 days), or the year, respectively.

**Entrainment** In the context of this study, entrainment is the synchronization of a biological oscillation to a Zeitgeber so that both have the same period.

**Free-running period ( r )** The period of an endogenous oscillator revealed in the absence of a Zeitgeber (e.g. at constant temperature, and in continuous darkness DD or continuous light LL) See Figure 18.

| Measurement | Troughs | Peaks |
|---|---|---|
| **General** | | |
| Body temperature | 04h00 – 08h00 | 18h00 – 22h00 |
| Blood pressure | 02h00 – 06h00 | 09h00 – 16h00 |
| Pulse rate | During sleep | Varying |
| Breathing rate | 04h00 – 08h00 | Varying |
| Airway resistance | 14h00 – 18h00 | 04h00 – 06h00 |
| Leucocyte count | ca 12h00 | ca 24h00 |
| **Urine** | | |
| Chloride | 24h00 – 6h00 | 12h00 – 18h00 |
| Calcium | 21h00 – 3h00 | 09h00 – 15h00 |
| Potassium and Sodium | 24h00 – 06h00 | 12h00 – 18h00 |
| Phosphate and urea | 06h00 – 10h00 | 19h00 – 14h00 |
| PH | Night | Day |
| **Hormones in blood** | | |
| Adrenaline | ca 02h00 | 12h00 – 20h00 |
| Antidiuretic hormone | Varying | 24h00 – 04h00 |
| Renin /aldosterone | ca 24h00 | ca 8h00 |
| Corticotropin/cortisol | ca 24h00 | ca 8h00 |
| Parathyroid hormone | 8h00 | ca 24h00 |
| Growth hormone | 04h00 – 08h00 | 90 minutes after onset of sleep/during exercise |
| Prolactin | Day | During sleep/exercise |
| Follitropin/Luteotropin/Testosterone | Day | During sleep |
| Thyrotropin | 10h00 – 16h00 | 22h00 – 24h00 |
| Melatonin | Awake (light) | Asleep (dark) |
| **Life phases** | | |
| Fetal movements | Before noon | Bedtime(mother) |
| Onset spontaneous labour | ca 12h00 | ca 24h00 |
| Death(non-traumatic) | ca 24h00 | ca 6h00 |

Table 4: Examples of circadian rhythms in humans (142).




Reference time: 199001010000

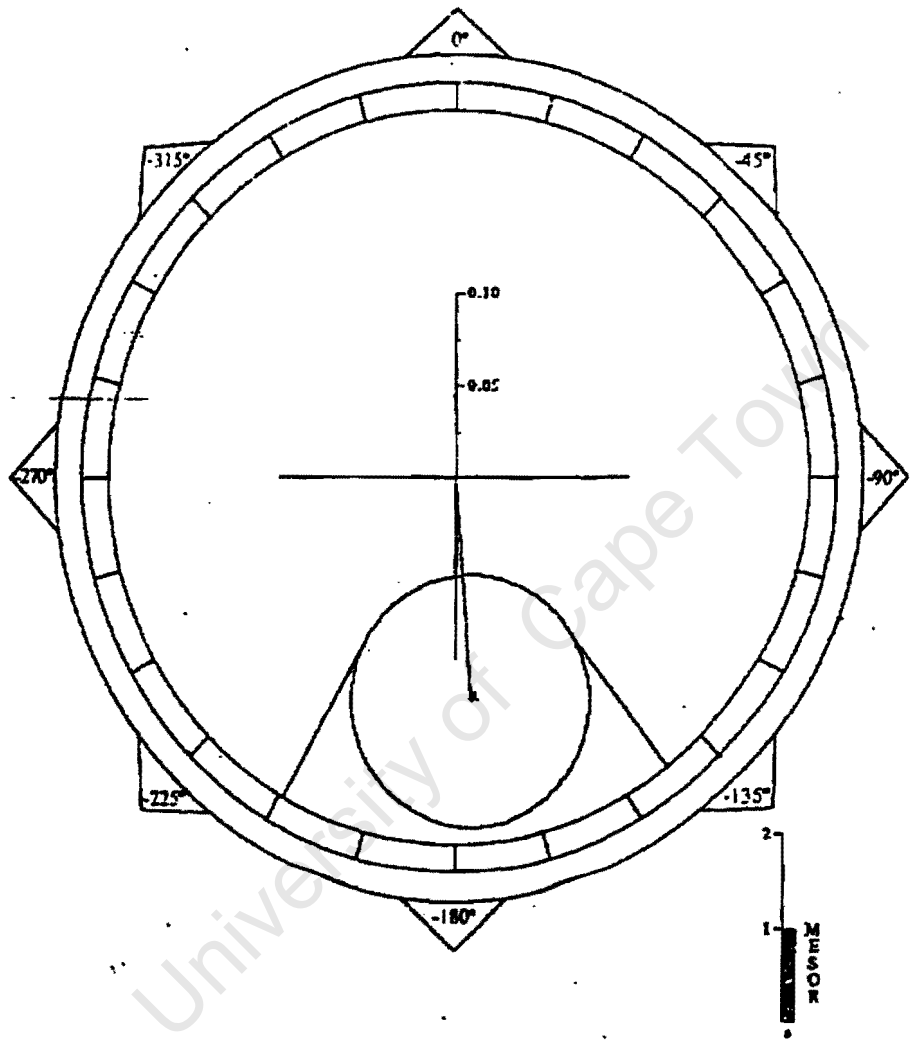
Single cosinor

Fitted period (h) = 8766.000

| Key | #pts | PR | P-value | MESOR ± SE | | AMP ± SE | | ACR ± SE | |
|---|---|---|---|---|---|---|---|---|---|
| a — a | 12 | 75.4 | 0.002 | 1.01 | 0.02 | 0.12 | 0.0 | -175.9 | 10.9 |



Figure 16 : Cosinor analysis of data as a Chronogram (144).




Single cosinor Period = 12 months = 360°

| Key | #pts | PR | P-value | MESOR | SE | AMP | Ci | ACR | Ci |
|---|---|---|---|---|---|---|---|---|---|
| a Legend | 12 | 75.4 | 0.002 | 1.01 | 0.02 | 0.12 | ( 0.1, 0.2) | -175.9 | (-142.3,-209.5) |

Figure 17 : Cosinor analysis of data as a polar cosinor plot (144).

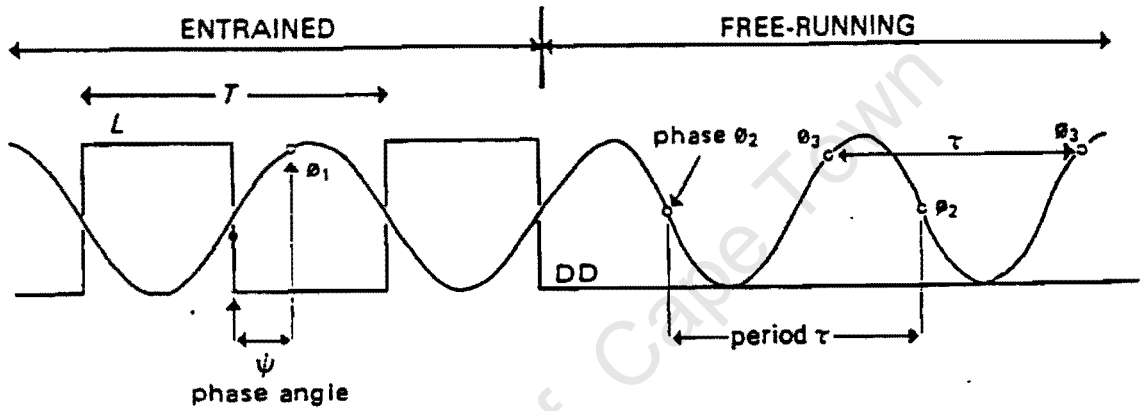





Figure18: A biological oscillation ( sine wave ) firstly entrained by an environmental Zeitgeber ( square wave ), and then free-running in constant darkness. (145)

Zeitgeber (square wave). and then free-running in constant darkness.
D = dark; $L$ = light; DD = constant darkness; $T$ = period of Zeitgeber (in this case one "dawn" to the next. 24 hours).
● - a phase point of the Zeitgeber oscillation ("dusk").
o- different phase points of the biological oscillation ($ø_1$,$ø_2$ etc).
$ø$ = phase; $\tau$ = period of oscillation in free-run measured from one phase ($ø_1$) to its next occurrence. Note that in this illustration $\tau$ in free-run is less than 24 hours.
$\psi$ = phase angle, in this illustration the phase angle between dusk and $ø_1$.

**Mesor** Midline estimating statistics of rhythm - adjusted mean over the period.

**Period** The time after which a definite phase reoccurs. In biological systems it should be stated which overt phase is being used to determine period (e.g. onset of activity, median of eclosion peaks, etc.)

**Phase ( Ø )** The instantaneous state of an oscillation within a period. In a circadian rhythm it may be the onset of locomotor activity, the point of sensitivity to light, etc.

**Phase angle (ψ)** The phase relationship between two phases on the same or different oscillations, normally measured in hours or in fractions of the circadian period.

**Phase response curve (PRC)** A plot of phase shift (magnitude and sign) caused by a single perturbation (i.e. light or temperature pulses) at different circadian phases (circadian times ) of an oscillator in free-run.

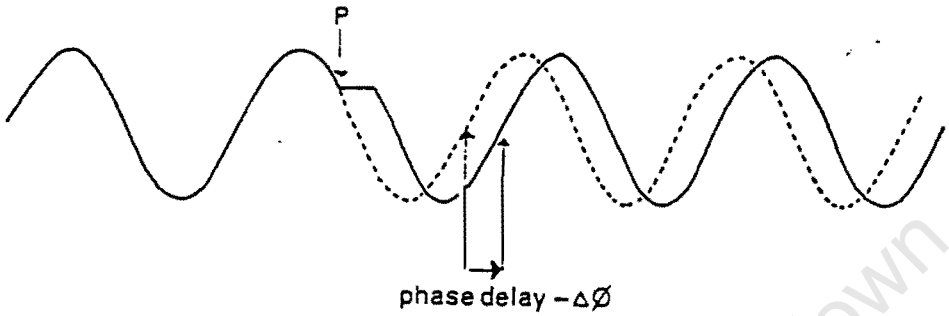
**Phase shift** (∅ ⊿)A single displacement of an oscillation along the time – axis following a perturbation. It may involve either an advance (+⊿Ø ) or a delay (-⊿Ø). See Figures 19 and 20.

**Photoperiod** The period of light in a daily cycle (day length), measured in hours.

**Photoperiodic counter** That aspect of the photoperiodic response, which consists of a temperature-compensated mechanism, which accumulates "information" from successive photoperiodic cycles.

**Photoperiodic response curve** The response of a population of an organism to a range of stationary photoperiods (DD to LL) usually including the critical day length.

**Range of entrainment** Range of frequencies in which a biological oscillation can be entrained by a Zeitgeber. For most organisms the range (for circadian rhythms) is 18 - 30 hours.




Figurel9: A biological oscillation in free-run subjected to a perturbation P causing a delay phase shift. (145)

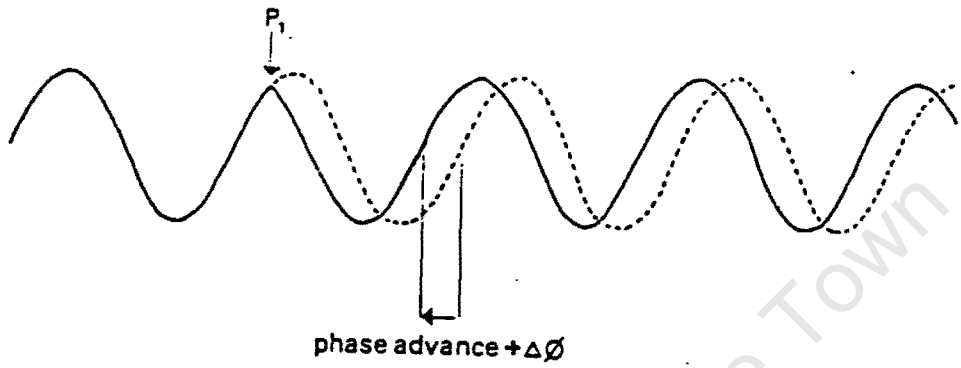





Figure 20: A biological oscillation in free-run subjected to a perturbation $P_1$, causing an advance phase shift. (145)

**Raster plot** Horizontal 24-hour segments of locomotor activity are plotted consecutively beneath one another. Thus line one refers to data for day one; line two refers to data for day two, etc.

**Skeleton photoperiod** A light regime using two shorter pulses of light to simulate dawn and dusk effects of a longer complete photo-period. Skeleton photoperiods may be either symmetrical (i.e. composed of two pulses of equal duration) or asymmetrical.

**Thermo period** A daily temperature cycle.

**Transients** One or more temporarily shortened or lengthened periods following perturbation by a light or temperature pulse.

**Zeitgeber (time-giver)** The forcing oscillation, which entrains a biological oscillation, the environmental cycles of light and temperature, tide,moonlight and season ( 125)(142)(143)(144)(145).

## 6.2. SOME COMMONLY USED ABBREVIATIONS IN CHRONOBIOLOGY

L Light fraction of cycle

D Dark fraction of cycle

LD Light/dark cycle

LL Continuous light

DD Continuous darkness

LD 12 :12 Represents 12 hours of light and 12 hours of darkness

$\tau$ Natural period of biological oscillator

T Period of Zeitgeber

Q Phase point

$\psi$ Phase angle

$-\Delta \emptyset$ Phase delay

$+\Delta \emptyset$ Phase advance

Ct Circadian time

Zt Zeitgeber time

(145).

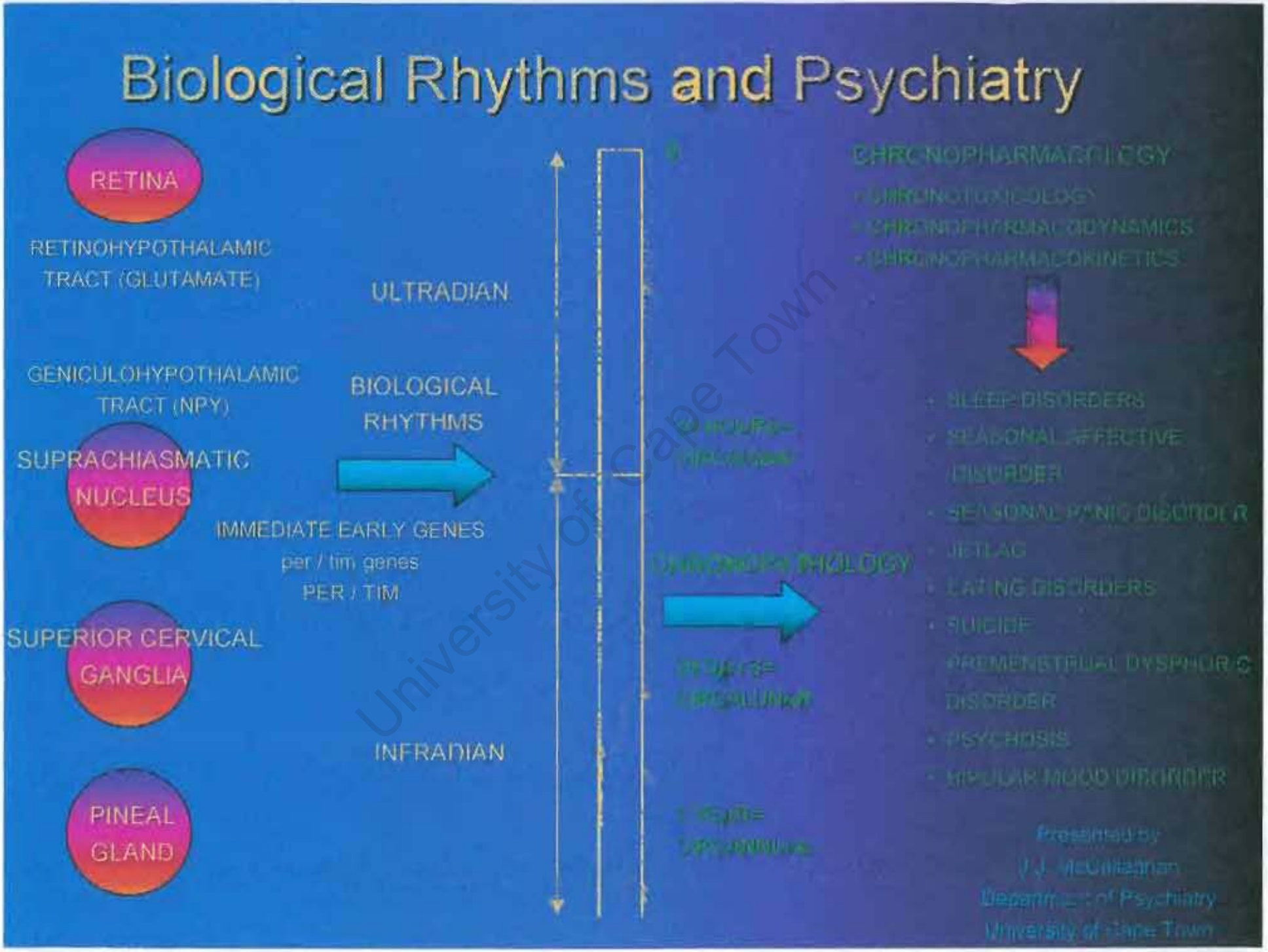
# *ADDENDUM*

1. Poster Presentation 12th National Psychiatry Congress September 2002

2. Presentation Psychopharmacology Congress September 2001

3. Academic and case discussion UCT July 2001

# Biological Rhythms and Psychiatry



# AN INVESTIGATION INTO THE ANXIOLYTIC PROPERTIES OF MELATONIN IN HUMANS.

McCALLAGHAN JJ

DEPARTMENT OF PSYCHIATRY, UNIVERSITY OF CAPE TOWN

Introduction
Melatonin, an indoleamine, is secreted by the pineal gland at night. It is postulated that abnormal melatonin physiology is involved in seasonal affective disorder, seasonal panic disorder, circadian rhythm related sleep disorder and jetlag. The anxiolytic properties of melatonin is however poorly documented.

Materials and Method
Thirty patients complaining of anxiety participated in an "N of 1" randomised double blind, placebo controlled trial of melatonin as an anxiolytic.

Results
Of the 27 patients that completed the trial, 15 patients reported lower than baseline scores in both periods during the melatonin exposure. However, 20 patients showed lower scores during both periods of their exposure to the placebo. A cross comparison of all responses revealed that there was a statistically significant reduction in anxiety during Pair1/Period1 (Melatonin), Pair2/Period1(Melatonin) and Pair2/period2(Placebo).

Conclusion
No conclusive evidence regarding Melatonin's anxiolytic properties was established. It seems that an "N of 1" study design may not be suitable as it does not allow for the possible shift in Melatonin phase response that may have a carry over effect on assessments in the next period.



UNIVERSITY OF CAPE TOWN
DEPARTMENT OF PSYCHIATRY AND MENTAL HEALTH
ACADEMIC LECTURES AND CASE DISCUSSIONS
JULY – OCT 2001

**Lectures and discussions on psychiatric, psychological and allied topics will be held as indicated on TUESDAYS at 12H45 IN THE AUDITORIUM, EDUCATION BUILDING, VALKENBERG HOSPITAL. These are open to all mental health professional, university and hospital clinical staff.**

(Enquiries: 4042164)

**JULY**

| | |
|---|---|
| 17 | **"Effective Child management within the family setting"**<br>MS CELESTE VAN DER MERWE, Programme and Training Manager, The Parent Centre, Claremont |
| 24 | **"Anxiolytic properties of melatonin in humans"**<br>DR J MCCALLAGAN, Department of Psychiatry, UCT |
| 31 | **"HIV drugs in the community – Can we do it?; Compliance and other factors"**<br>DR LINDA GAIL-BEKKER, Infectious Diseases Unit, Faculty of Health Sciences, UCT |

**AUGUST**

| | |
|---|---|
| 7 | **" The Self in motion : its expression in music and dance"**<br>MS HELEN HENDERSON, Music Therapist |
| 14 | **" Interparental conflict and child adjustment"**<br>DR LAUREN WILD, Research Fellow, Dept of Psychiatry, UCT |
| 21 | **"Directions of Mental Health Services in the Western Cape – An overview"**<br>MS SHARON KLEINTJIES, Programme Director Mental Health, PAWC |
| 28 | **"Primary Health Care Lead Theme – A discussion on the Faculty's intention"**<br>PROF JD BAQWA, Dept. of Primary Health Care, UCT. |

## REFERENCES

1. Klawans, H.L. *Why Michael couldn't hit. And other tales of the neurology of Sports.* W.H. Freeman 1996; p 6 - 10.

2. Stahl, S.M. *Essential Psychopharmacology. Neuroscientific basis and Practical applications* . 2nd edition. Cambridge University Press 2000; p 3 - 6.

3. Anton, H. *Elementary Linear Algebra.* 6th edition. John Wiley and sons Inc 1999; p 67 - 69.

4. Sperry, R.W. *Neurology and the Mind-Brain Problem.* In Robinson, T.E. (ed.) *Behavioral Approaches to Brain Research.* Oxford University Press 1983; p 27 -29.

5. Donovan, B.T. *Humors, Hormones and the Mind. An approach to the understanding of Behaviour.* Stockton Press 1988; p 158 - 159.

6. Reinberg, A., Smolensky, M.H. *Introduction to Chronobiology.* In *Biological rhythms and Medicine. Cellular, Metabolic, Psychopathologic and Pharmacological Aspects.* Springer-Verlag 1983; p 1 - 17.

7. McEachron, D.L . *Hormones, Rhythms and the Blues.* In: Schultin, J. (ed ) *Hormonally induced changes in Mind and Brain.* Academic Press 1993; p 291.

8. Bloom, S.E., Lazerson, A. *Brain, Mind and Behaviour.*2nd ed. W.H. Freeman and Company 1988; p 170 -205.

9. *Dorland's illustrated Medical Dictionary.* 26th edition. W.B.Saunders Company 1981; 65, p 228, 268.

10. Hastings, M. *The brain, circadian rhythms, and clock genes.* BMJ 317 1998; 1704 - 1707.

11. Fitzgerald, M.J.T. *Neuroanatomy. Basic and clinical.*3rd ed. W.B. Saunders Company 1996; p 205 - 2ll.

12.Hamilton, W.J., Morsman, H.W. *Human Embriology*. 4th ed. W Heffer and Sons Ltd. The Williams and Willers Company 1972; p 437 - 460.

13. Adams, R.D., Victor, M. *Principles of Neurology*. 5th edition. McGraw-Hill 1993; p 443 - 456.

14. Erlich, S.S., Apuzzo, M.L.J. *The pineal gland: anatomy, physiology, and clinical significance*. J. Neurosurg 1985: 63; 321 - 341.

15. Card, P.J., Moore, R.Y. *The organization of visual circuits influencing the circadian activity of the suprachiasmatic nucleus*. In Klein, D.C., Moore, R.Y., Reppert, S.M. (Ed). *Suprachiasmatic nucleus. The mind's clock.* Oxford University Press 1991; p 51- 76.

16. Watts, A.G. *The efferent projections of the suprachiasmatic nucleus: anatomical insights into the control of circadian rhythms*. In Klein, D.C., Moore, R.Y., Reppert, S.M. (Ed). *Suprachiasmatic nucleus. The mind's clock.* Oxford University Press 1991; p 77 - 106.

17 . Majzoub, J.A., Robinson, B.G., Emanuel, R.L. *Suprachiasmatic nuclear rhythms of Vasopressin MRNA in vivo*. In Klein, D.C., Moore, R.Y., Reppert, S.M. (Ed) *Suprachiasmatic nucleus. The mind's clock.* Oxford University Press 1991; p 177 - 190.

18. Albers, H.E., Lion S-Y., Ferris, C.F., Stopa, E.G., Zoeller, R.T. *Neurochemistry of circadian timing*. In Klein, D.C., Moore, R.Y., Reppert, S.M. (Ed) *Suprachiasmatic nucleus. The mind's clock*. Oxford University Press 1991; p 263 - 288.

19. Yudofsky, S.C., Hales, R.E. (Ed) *The American Psychiatric Press Textbook of Neuropsychiatry*. 2nd Ed,. American Psychiatric press, Inc. 1998; p 34.

20. Gillian, T.C., Kendall, E.R., Jessel, T.M. *Genes and Behavior*. In Kendall, E,R., Schwartz, J.A., Jessel, T.M. (ed) *Principles of Neural Science*. 4th edition McGraw-Hill 2000; p 36 – 62.

21. Gekakis, N., Staknis, D., Nguyen, H.B. et al. *Role of the CLOCK Protein in the Mammalian circadian Mechanism*. Science 1998: 280; 1564.

22. Barinaga, M. *New clock gene cloned.* Science 1995: 270; 732 - 733.

23. Barinaga,M. *Researchers find the reset button on the fruit fly clock.* Science 1996: 271; 1671.

24. Myers, M.P., Wager - Smith, K., Rothenfluh - Hilfiker, A. et al. *Light – induced Degradation of TIMELESS and Entrainment of the Drosophila Circadian Clock.* Science 1996: 271; 1736, 1739.

25. Kronauer, R.E., Czeisler, C.A., Pilato, S.F. et al. *Mathematical model of the human circadian system with two interacting oscillators.* Am. J. Physiol. 1982: 242; R3 - R21.

26. Arendt, J. *Melatonin and the Mammalian Pineal Gland.* Chapman and Hall. 1st edition 1995; p 66 - 109.

27. Carpenter, M.B. *Core text of Neuroanatomy.*2nd edition. The Williams and Williams Company 1978; p 434 - 461 .

28. Oksche, A. *The development of the concept of photoneuroendocrine systems: Historical perspective*. In Klein, D.C., Moore, R.Y., Reppert, S.M. (Ed). *Suprachiasmatic nucleus. The mind's clock.* Oxford University Press 1991; p 5 –10.

29.Yu, H-S., Tsin, A. T. C., Reiter, R.J. *Melatonin: History, Biosynthesis and Assay Methodology.* In Yu, H-S. and Reiter, R.J. (Ed) *Melatonin. Biosynthesis, Physiological effects and Clinical Applications.* CRC Press. 1993; p 1 - 16.

30. Weaver, D.R., Rivkees, S.A., Carlson, L.L. et. al. *Localization of melatonin in mammalian brain.* In Klein, D.C., Moore, R.Y., Reppert, S.M. (Ed) *Suprachiasmatic nucleus. The mind's clock.* Oxford University Press 1991; p 289 - 308.

31. Cassone, V.M. *Melatonin and Suprachiasmatic nucleus function.* In Klein, D.C. Moore, R.Y., Reppert, S.M. (Ed) *Suprachiasmatic nucleus. The mind's clock.* Oxford University Press 1991; p 309 - 310.

32. Morgan, P.J., Barrett, P., Howell, E., et al. *Melatonin receptors: Localization, molecular pharmacology, and physiological significance.* Neurochem Int. 1994: 24(2); 101 - 146.

33. Ebadi, M. *Multiple pineal receptors in regulating melatonin synthesis.* In Yu, H-S. and Reiter, R.J. (Ed) Melatonin. *Biosynthesis, Physiological effects and Clinical Applications.* CRC Press 1993; p 39 - 71.

34. Burton, S., Daya, S., Potgieter, B. *Melatonin modulates apomorphine-induced rotational behavior.* Experientia 1991: 47; 466 - 469.

35. Sandyk, R., Kay, S.R., Gillman, M.A. *The role of melatonin in the anti-psychotic and motor side effect of neuroleptics: a hypothesis.* Intern J. Neuroscience 1992: 64; 203 - 207.

36. Reiter, R.J. *The melatonin rhythm: both a clock and a calendar.* Experientia 1993: 49; 654 - 664.

37. Duman, R.S. *Windows on the human brain and the neurobiology of psychiatric illness* (editorial). Neuropsychopharmacology 2002: 26(2); 141 - 142.

38. Lewis, D.A. *The human brain revisited : Opportunities and challenges in post mortem studies of psychiatric disorders.* Neuropsychopharmacology 2002: 26(2); 143 – 154.

39. College of Medicine of South Africa. *Guidelines for the Fellowship of the College of Psychiatrists of SA.* 1999.

40. Wehr, T.A. *Seasonal Affective Disorder: A Historical overview.* In Rosenthal, N.E., Blekor, M.C. (ed) *Seasonal Affective Disorder and Phototherapy.* Guilford Press 1989; p 11-31.

41. Rosenthal. N.E., Sack, D.A., Gillin, D.A. et al. *Seasonal Affective Disorder: a description of the syndrome and preliminary findings with light therapy.* Arch Gen Psych 1984 : 41 ;72 - 80.

42.Wehr, T.A., Schultz, P.M. et al. *Contrasts between symptoms of Summer Depression and Winter depression.* Journal of Affective Disorders 1991: 23; 173 - 183.

43.Takahashi, K., Asano, Y., Kohsaka, M. et al. *Multi -center study of Seasonal Affective Disorder in Japan.* J. Affect. Disorder 1991:21; 57 – 65.

44. Wehr, T.A., Rosenthal, N.E. *The Seasonality of affective illness.* Am. J. Psychiatry 1989: 146; 829 - 839.

45. Depue, R.A., Arbisi, P., Spoont, M.R. et al. *Dopamine functioning in the Behavioral Facilitation System and Seasonal Variation in behavior: Normal population and clinical studies.* In Rosenthal, N.E., Blekor, M.C. (ed) *Seasonal Affective Disorder and Phototherapy.* Guilford Press 1989; p 230 – 259.

46. Wehr, T.A., Duncan, W.C., Sher, L. et al. *A circadian signal of change of Season in patients with Seasonal Affective Disorder.* Arch Gen Psych 2001: 58; 1108 - 1114 .

47. Wehr, T.A., Moul, D.E., Giesen, H.A. *Conservation of photoperiod responsive mechanisms in humans.* Am J Physiol 1993: 265; R846 - R857.

48. Wehr, T.A., Giesen, H.A., Moul, D.E. et al. *Suppression of human responses to seasonal changes in day length by modern artificial lighting.* Am J Physiol 1995: 269; R173 - RI78.

49. Remè, C.E., Terman, M., Wirz-Justice, A. *Are deficient retinal photoreceptor renewal mechanisms involved in the pathogenesis of major depression?* Arch Gen Psych 1990: 47; 878 - 879 .

50. Terman, M. *Internal Night* ( commentary). Arch Gen Psych 2001: 58; 1115 - 1116.

51. Terman, M., White, T.M., Jacobs, J. *An Automated Morningness-Eveningness Questionnaire ( AutoMEQ).* 2003 Center for Environmental Therapeutics Website , available at www. cet.org/AutoMEQ.htm

52. O'Rourke, D.A., Wurtman, J.J., Brzezinski, A. et al. *Serotonin implicated in Etiology of Seasonal Affective Disorder.* Psychopharmacology Bulletin 1987: 23(3); 358 - 359.

53. Jacobson, F.M., Sack, D.A., Wehr, T.A. et al. *Neuroendocrine response to 5- Hydroxytryptophan in Seasonal Affective Disorder.* Arch Gen Psych 1987: 44; 1086 - 1091.

54. Checkley, S. *Neuroendocrinology.* In Paybel, E.S. (Ed) *Handbook of Affective Disorders.* Churchill Livingstone 1992: p 255 - 266.

55. Oren, D.A., Rosenthal, N.E. *Seasonal Affective Disorders.* In Paybel, E.S.(ed) *Handbook of Affective Disorders.* Churchill Livingstone 1992: p 551 - 567.

56. Lam, R.W., Tam, E.M., Greval, A. et al. *Effects of Alpha - Methyl - Para - Tyrosine Induced Catecholamine Depletion in Patients with Seasonal Affective Disorder in Summer Remission.* Neuropsychopharmacology 2001: 25(S5); S99 - S101.

57. Mersch, P.P.A., Middendorp, H.M., Bouhuys, A.L. et al. *Seasonal Affective Disorder and Latitude: A review of the literature.* Journal of Affective Disorders 1999: 53; 35 - 48.

58. Raheja, S.K., King, E.A., Thompson, C. *The Seasonal Pattern Assessment Questionnaire for identifying seasonal affective disorders.* Journal of Affective Disorders 1996: 41;193 - 199.

59. Magnusson, A. *Validation of the Seasonal Pattern Assessment Questionnaire (SPAQ).* Journal of Affective Disorders 1996:40;121 - 129.

60. Magnusson, A., Friis, S., Opjordsmoen, S. *Internal Consistency of the Seasonal Pattern Assessment Questionnaire (SPAQ).* Journal of Affective Disorders 1997: 42; 113 - 116.

61. Eagles, J.M., Howie, F.L., Cameron, I.M. et al. *Use of Health Care Services In Seasonal Affective Disorders.* British Journal of Psychiatry 2002: 180; 449 - 454.

62. Kendrick, T. *Seasonal Affective Disorder among general practice attendees.* British Journal of Psychiatry 2002: 180; 394 - 395 .

63. Michalak,E.E., Wilkinson, C., Dowrick, C., Wilkinson, G. *Seasonal Affective Disorder : prevalence, detection and current treatment in North Wales.* British Journal of Psychiatry 2001: 179; 31 - 34.

64. Sandyk, R., Dann, L.C. *Seasonal Panic Disorder: a possible variant of Seasonal Affective Disorder.* Intern. J. Neuroscience 1992: 62; 263 -267.

65. Geraci, M.F., Uhde, T.W. *Diurnal Symptoms and Severity in Panic Disorder: A Preliminary Study of 24-hour changes in Panic attacks, Generalized Anxiety and Avoidance Behaviour.* British Journal of Psychiatry 1992: 161; 512 – 516.

66. Halle, M.T., Dilsaver, S.C.*Comorbid Panic Disorder in Patients with Winter Depression.* Am J Psychiatry 1993: 150(7); ll08 - 1109.

67. Altemus, M., Pigott, T., Kalogeras, K.T. et al. *Abnormalities in the Regulation of Vasopressin and Corticotrophin Releasing Factor Secretion in Obsessive-Compulsive Disorder.* Arch Gen Psychiatry 1992: 49; 9 -20.

68. Altemus, M., Pigott, T., L'Heureux, F. et al. *CSF Somatostatin in Obsessive - compulsive Disorder.* Am J Psychiatry 1993: 150(3); 460 - 464.

69. Yoney, T.H., Pigott, T.A., L'Hereux, F. et al. *Seasonal variation in Obsessive-Compulsive Disorder : Preliminary Experience with Light Therapy.* Am J Psychiatry 1991: 148(12); 1727 - 1728.

70. Silverton, J.A. *Something new under the sun: Comments on Gerald Russell's "Anorexia Nervosa through time ".* In Szmakler, G., Dare, C., Treasure, J. (ed) *Handbook of Eating Disorders. Theory, Treatment and Research.* John Wiley and sons 1995; p 25 - 27.

71. Katzman, D.K. *Prevention of medical complications in children and adolescents with Eating Disorders.* In Piran, N., Levin, M.P., Steiner - Adam, C. (Ed*) Preventing Eating Disorders. A Handbook of Intervention and special Challenges.* 1999. Brunner /Mazel; p 304 - 318.

72. Robinson, P.H., McHugh, P.R. *A physiology of starvation that sustains eating disorders.* In Szmakler, G., Dare, C., Treasure, J. (ed) *Handbook of Eating Disorders. Theory, Treatment and Research.* John Wiley and sons 1995; p 109.

73. Le Fur, C., Romon, M., Lebel, P. et al. *Influence of mental stress and Circadian cycle on postprandial lipemia.* Am J Clin Nutr, 1999: 70; 213 - 220.

74. Birketvedt, G.S., Florholmen, J., Sundsfjord, J. *Behavioural and neuroendocrine characteristics of Night - eating Syndrome.* JAMA, 1999: 282; 657 - 663.

75. Altemus, M., Hetherington, M.M., Flood, M. et al. *Decrease in Resting Metabolic rate during abstinence from bulimic behaviour.* Am J Psychiatry 1991: 148; 1071 - 1072.

76. Berman, K., Lam, R.W., Goldner, E.M. *Eating attitudes in seasonal affective disorder and bulimia nervosa.* Journal of Affective disorders. 1993: 29; 219 - 225.

77. Robinson, P.H., Checkley, S.A., Russel, G.F.M. *Suppression of eating by Fenfluramine in patients with Bulimia Nervosa.* British Journal of Psych 1985: 146; 169 - 176.

78. Lam, R.W., Goldner, E.M., Solyom, L. et al . *A controlled study of Light Therapy for Bulimia Nervosa.* Am J Psychiatry 1994: 151; 744 - 750.

79. Parry, B.L., Newton, R.P. *Chronobiological Basis of Female - specific Mood Disorders.* Neuropsychopharmacology 2001: 25; S102 - S108.

80. Epperson, C.N., Haga, K., Mason, G.F. et al. *Cortical 8 - Aminobutynic acid Levels across the menstrual cycle and those with premenstrual Dysphoric Disorder.* Arch Gen Psych 2002: 59; 851 - 858.

81. Sundstrom, I., Nyberg, S., Backstrom, T. *Patients with premenstrual syndrome have reduced sensitivity to midazolam compared to control subjects.* Neuropsychopharmacology 1997: 17; 370 - 381.

82. Halbreich, U., Endicott, J., Nee, J. *Premenstrual depressive changes.* Arch Gen Psychiatry 1983: 40; 535 - 542.

83. Brayshaw, N.D., Brayshaw, D.D. *Thyroid hypofunction in premenstrual syndrome.* The New England Journal of Medicine 1986: 40 (23).

84. Muse, K.N., Cetel, N.S., Futterman, L.A. et al . *The Premenstrual Syndrome. The facts of "Medical Ovarectomy".* The New England Journal of Medicine 1984: 311(21);1345 - 1349.

85. Yonkers, K.A., Halbreich, U., Freeman, E. et al. *Sertraline in the treatment of Premenstrual Dysphoric Disorder.* Psychopharmacology Bulletin 1996: 32(l); 41 - 46.

86. Ehlers, C.L., Frank, E., Kupfer, D.J. *Social Zeitgebers and biological rhythms. A unified approach to understanding the etiology of Depression.* Arch Gen Psych 1988: 45; 948 - 952.

87. Sclare, P., Creed, F. *Life events and the onset of mania.* B J Psychiatry 1990: 156; 508 - 514.

88. Malkoff-Schwartz, S., Frank, E., Anderson, B. et al. *Stressful life events and Social Rhythm Disruption in the onset of manic and Depressive Bipolar Episodes.* Arch Gen Psych 1998: 55; 702 -707.

89. Ambelas, A. *Life events and Mania. A special relationship?* British Journal of Psychiatry 1987: 150; 235 -240.

90. Durheim, E. *Le Suicide*. Paris. 1897. Translated by Spalding, J.E., Simpson, E. as *Suicide : a study in Sociology* 1952. Routledge and Kega Paul, London.

91. Hakko, H., Rasanen, P., Tiihonen, J. *Seasonal variation in suicide occurrence in Finland.* Acta Psychiat. Scand. 1998: 98; 92 -97.

92. Flischer, A.J., Parry, C.D.H., Bradshaw, D. et al. *Seasonal variation in suicide in South Africa.* Psychiatric Research 1997: 66; 13 - 22.

93. Bradvik, L., Berglund, M. *Seasonal distribution of suicide in alcoholism.* Acta Psychiat. Scand. 2002: 106; 299 - 302.

94. Yip, P.S.F., Chao, A., Chiu, C.W.F. *Seasonal variation in suicides : Diminished or vanished. Experience from England and Wales 1982 - l 996.* B J Psychiatry 2000: 177; 366 - 369.

95. Symonds, R.L., Williams, P. *Seasonal variation in the incidence of mania.* B J Psychiatry 1976: 129; 45 - 49.

96. Lewy, A.J., Wehr, T.A., Goodwin, F.K. et al . *Manic depressive patients may be supersensitive to light.* The Lancet 1981: 14; 383 - 394.

97. Silverstone, T., Romans, S., Hunt, N. et al. *Is there a seasonal pattern of Relapse in Bipolar Affective Disorder? A Dual North and Southern Hemisphere Cohort Study.* B J Psychiatry 1995: 167; 58 - 60.

98. Thompson, C., Stinson, D., Fernandez, M. et al. *A Comparison of normal, bipolar and seasonal affective disorder subjects using the Seasonal Pattern Assessment Questionnaire.* Journal of Affective Disorders 1988: 14; 257 - 264.

99. Reynolds, T.D., London, W.P., Yorke, J.A. *Behavioral rhythms in schizophrenia.* The Journal of Neurons and Mental disease 1998: 166(7); 489 - 499.

100. Takei, N., O' Callaghan, E., Sham, P. et al. *Seasonality of admissions in the Psychoses : effect of diagnosis, sex, and age at onset.* B J Psychiatry 1992: 161; 506 - 511 .

101. Hofman, M.A . *The Human Circadian Clock and Ageing.* Chronobiology International 2000: 17(3); 245 - 259.

102. Copinschi, G., Spiegel, K., Leproult, R. et al. *Pathophysiology of human circadian rhythms.* Novartis Foundation Symposium 2000: 227; 143 - 162.

103. Wehr, T.A., Sack, D.A., Rosenthal, N.E. *Sleep Reduction as a final common Pathway in the Genesis of Mania.* Am J Psychiatry 1987: 144(2); 201 - 203.

104. Irwin, M. *Neuroimmunology of Sleep in Depression and Alcoholism.* Neuro- Psychopharmacology 2001: 25; 545 - 549.

105. Salin-Pascual, R., Gerashchenko, D., Greco, M. et al. *Hypothalamic regulation of Sleep.* Neuropsychopharmacology 2001: 25; 521 - 527.

106. Mignot, E. *A Commentary on the neurobiology of the Hypocretin/orexin system.* Neuropsychopharmacology 2001: 25; 505 - 513.

107. Siegel, J.M., Moore, R., Thannickal, T. et al. *A Brief History of Hypocretin/orexin and Narcolepsy.* Neuropsychopharmacology 2001: 25; 514 - 520.

108. Tonin, G., Cirelli, C. *Modulation and Gene Expression during Sleep and wakefulness: a review of recent findings.* Neuropsychopharmacology 2001: 25; 528 - 535.

109. Moore, C.A., Williams, R.L., Hirskowitz, M. *Sleep Disorders.* In Sadock, B.J. and Sadock, V.A. (Ed) *Comprehensive Textbook of Psychiatry.* 7th ed. Lippincott Williams & Wilkens, 2000; p 1677 – 1700.

110. Spitzer, R.L., Terman, M., Williams, J.W.B. et al. *Jetlag : Clinical features, Validation of a new syndrome- specific scale and lack of response to Melatonin in a Randomized, Double blind trial.* Am J Psychiatry 1999: 156(9); 1392 - 1396.

111. Kripke, D.F., Garfinkel, L., Wingard, D.L. et al. *Mortality associated with Sleep Duration and Insomnia.* Arch Gen Psychiatry 2002: 59; 131 - 136.

112. Toh, K.L., Jones, C.R., He, Y. et al. *An hPER2 Phosphorylation Site Mutation in familial Advanced Sleep Phase Syndrome.* Science 2001: 291; 1040 - 1043.

113. Horne, J.A. *Human Sleep, Sleep loss and behaviour. Implications for the prefrontal cortex and psychotic disorder.* B J Psychiatry 1993: 162; 413 - 419.

114. Krauchi, K., Wirz-Justice, A. *Circadian clues to sleep onset mechanisms.* Neuropsychopharmacology 2001: 25; 592 - 596.

115. Farmer, S. *Neural rhythms in Parkinson's Disease* (Editorial). Brain 2002: 125; 1175 - 1176.

116. Turek, F.W., Dugovic, C., Zee, P.C. *Current understanding of the Circadian Clock and the clinical implications for neurological disorders.* Ach Neurol 2002: 58; 1781 - 1787.

117. Danesi, M.A. *Seasonal variations in the incidence of photoporoxysmal response to stimulation among photosensitive epileptic patients: evidence from repeated EEG recording.* Journal of Neurology, Neurosurgery and Psychiatry 1988: 51; 875 - 877.

118. Newmark, M.E., Penny, J.K. *Catamenial Epilepsy: A Review.* Epilepsion 1980: 21; 281 - 300.

119. Wirz - Justice, A., Van den Hoofdakker, P. *Sleep deprivation in Depression: What do we know, where do we go?* Biological Psychiatry 1999: 46; 445 - 453.

120. Benedett, F., Colombo, C., Barbim, B. et al. *Ongoing Lithium treatment prevent relapse after total sleep deprivation.* J Clin Psychopharmacology 1999: 19; 240 - 245.

121. Leibenluft, E., Wehr, T.A. *Is sleep deprivation useful in the treatment of depression?* Am J Psych 1992: 149; 159 - 168.

122. Boivin, D.B., Czeisler, C.A., Dijk, D.J. et al. *Complex interactions of the sleep-wake cycle and circadian phase modulates mood in healthy subjects.* Arch Gen Psych 1997: 54; 145 - 152.

123. Monk, T.H. *What can the Chronobiologist do to help the shift worker?* J of Biol Rhythms 2000: 15(2); 86 - 94.

124. Wileman, S.M., Eagles, J.M., Andrew, J.E. et al. *Light therapy for Seasonal Affective Disorder in Primary Care.* B J Psychiatry 2002: 178; 311 - 316 .

125. Haus, E., Nicolau, G.Y., Lakutue, D. et al. *Reference values for Chronopharmacology.* Annu Rev Chronopharmacology 1988: 4; 333 - 424.

126. Nagayama, H. *The influence of Biological rhythms on the effect of psychotropic drugs.* Psychosomatic Medicine 1999: 61; 618 - 629.

127. Henauer, S., Lombrozo, L., Hollister, L.E. *Circadian variation of Lorazepam - induced neurological deficits.* Life Sciences 1984: 35(22); 2193 - 2197.

128. Lemmer, B. *Chronopharmacokinetics: Implications for drug treatment.* J Pharm Pharmacol 1999: 51; 887 - 890.

129 . Lemmer, B., Nold , G. *Circadian changes in estimated hepatic blood flow in healthy subjects.* British J Clin Pharmac 1991: 32; 627 - 629.

130. Nakano, S., Hollister, L.E. *Chronopharmacology of Amitriptyline.* Clin Pharmacol Ther 1983: 33(4); 453 - 459.

131. Pierrefiche, G., Zerbib, R., Laborit, H. *Anxiolytic activity of Melatonin in mice: involvement of benzodiazepine receptors.* Research Communications in Chemical Pathology and Pharmacology 1993: 82(2); 131 - 141.

132. McCallaghan, J.J. *Anxiolytic Properties of Melatonin in humans.* Unpublished MSc (Pharm) 1999.Rhodes University.

133. Sandyk, R. *Does Melatonin mediate the therapeutic facts of 5-HT reuptake inhibitors in Obsessive Compulsive Disorder?* Intern J Neuroscience 1992: 64; 221 – 223.

134. Dahlitz, M., Alvarez, B., Vignau, J. et al. *Delayed sleep phase syndrome response to melatonin.* The Lancet 1991: 337; 1121 - 1123.

135. Arendt, J. *Melatonin and the Mammalian Pineal gland.* Chapman and Hall 1st edition 1995; p 247 - 289.

136. Benedetti, F., Barbini, B., Campon, E. et al. *Sleep phase advance and Lithium to sustain the anti-depressant effect of total sleep deprivation in bipolar depression: new findings supporting the internal coincidence mode.* Journal of Psychiatric Research 2001: 35; 323 -329.

137. Wirz-Justice, A., Campbell, I.C. *Anti-depressant drugs can slow or dissociate circadian rhythms.* Experientia 1982: 38; 1301 - 1309.

138. Smolensky, M.H. *Knowledge and attitudes of American physicians and the Public about medical chronobiology and chronotherapeutics. Findings of Two Gallup surveys.* Chronobiology International 1998: 15(4); 377 - 394.

139. Strohl, K.P., Haponk, E.E., Sateia, M.J. et al. *The need for a knowledge system in sleep and Chronobiology (Commentary).* Academic Medicine 2000: 75(8); 819 - 821.

140. Prideaux, D. *Curriculum Design.* BMJ 2003: 326 ; 268 - 270.

141. Eagles, J.M. *Seasonal Affective Disorder.* British J Psychiatry 2003: 182; 174 – 176.

142. Lochner, J. de V. *Biorhythms - Mechanisms and clinical implications.* Continuing Medical Education Journal. 1994: 12; 1433 - 1443.

143. Bingham, C., Arbogast, B., Cornelissen, G. et al. *Inferential statistical methods for estimating and comparing cosinor parameters.* Chronobiology 1982: 9; 397 - 439.

144. Kock, H.J. *Cosinor modelling of suicides in Finland* ( letter to editor ). Acta Psychiat Scand 1999: 99; 309 - 310.

145. Saunders, D.S. *Biological Rhythms.* Blackie and Son Limited 1977: p 164 - 167.