PHOTOTHERAPY AS A TREATMENT FOR DEPRESSION : AN ANALYSIS OF THE THEORY AND RESEARCH.

A thesis presented in partial fulfillment of
the requirements for the degree of
Master of Science in Psychology
at Massey University.

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ABSTRACT

The efficacy of phototherapy as a potential treatment modality for certain types of depression is examined. Phototherapy is suggested to be useful in relieving depressive symptoms in individuals exhibiting circadian rhythm disturbances. Particular attention is paid to the characteristics of endogenous and seasonal depressives. Endogenous depressives exhibit phase-advances in the sleep-wake cycle, REM-sleep, temperature, cortisol, and melatonin rhythms. Preliminary evidence indicates phase-delays in the rhythms of seasonal depressives. A possible physiological pathway through which light may act upon circadian rhythm generators to correct rhythm abnormalities is discussed. Theoretical positions which have been proposed to explain the underlying mechanisms of phototherapy are evaluated. Research findings are discussed within these frameworks. Major experimental weaknesses limit the usefulness of many research findings as support for the effectiveness of phototherapy in treating depression. An attempt is made to clarify some of these problems and to highlight the methodological shortcomings of research in this area. Strategies for future research methodology are recommended. Better experimental design which controls for placebo effects is needed in order to properly evaluate the antidepressant effects of phototherapy.

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CHAPTER ONE: OVERVIEW

Prior to the 20th Century there were no recorded cases of successful somatic treatment of depression. Since then many physiological approaches have been developed to treat depressive disorders. At present pharmacological interventions are the usual mode of treatment. Unfortunately such therapy has not always proved successful and often produces undesirable side-effects.

In recent years a new form of therapy has been proposed to treat depressive disorders which are perceived to have a biological etiology. Some people with depressive disorders have been found to show marked disturbances of the circadian system. Phototherapy involves exposing these individuals to bright light in order to relieve depressive symptoms. The rationale is that bright light has a corrective action on the circadian system, leading to mood improvement.

Phototherapy has important implications for the treatment of depressed individuals with biological disturbances. Phototherapy, if effective, could be a relatively inexpensive and rapid mode of treatment which produces few side-effects.

The present thesis critically examines the efficacy of phototherapy as a treatment for certain types of depression. Chapter Two introduces the reader to circadian rhythms and terms fundamental to an understanding of the area. Chapter Three presents evidence for the ability of bright light to influence human circadian rhythms and suggests that light may follow a physiological pathway to directly affect circadian rhythm generators. The features of two subgroups of depressed individuals suggested to be likely responders to phototherapy are discussed in Chapter Four. General findings regarding the circadian disturbances specific to each group are presented. Chapter Five looks at the theories which have been proposed to explain the way in which light may work to relieve depression. Findings from studies of phototherapy are considered in terms of support for these theories followed by a critical evaluation of the research in Chapter Six. Finally, Chapter Seven presents suggestions for future studies in the form of a research design which attempts to improve upon those of previous studies and which could be used

to better evaluate the effectiveness of phototherapy in some types of depression. Other lines of research which could contribute substantially to the study of phototherapy are also discussed.

CHAPTER TWO: INTRODUCTION TO CIRCADIAN RHYTHMS AND DEFINITION OF TERMS

Rhythmicity is a fundamental property of living organisms. Rhythmical fluctuations occur at all levels of cellular complexity from unicellular to multicellular organisms in both the plant and animal kingdoms (Aschoff, 1963). Biological rhythms were observed as far back as the eighteenth century when De Mairan noted that the leaf movements of plants persisted in constant darkness (Bunning, 1964). However, it was some two hundred years before intensive investigation of these rhythms began. In humans there are rhythms which cycle once per fraction of a second (for example, the alpha waves produced by the brain), those which cycle once per several seconds (for example, the respiratory rhythm), through to those with a yearly cycle (Minors and Waterhouse, 1981).

In many organisms the rhythms which seem to predominate are those which are synchronized to a major environmental event such as the annual alternation of summer and winter. The long period of light, or photoperiod, provided by summer days is the cue for some animals to breed. Others breed only during the short photoperiod of winter. The seasonality of reproductive responses is itself a type of biological rhythm since many animals reproduce once a year. For most living beings, however, and certainly for humans, the most obvious environmental change is the alternation between day and night. In human beings habits of eating and drinking, rest and activity, and sleep generally follow a routine which is regulated by the 24-hour day-night cycle. Consequently, many human physiological, psychological, and biochemical processes cycle with a frequency close to that of the solar day. It is these cycles with periods close to 24-hours which have become known as circadian (circa = approximately, dies = day) rhythms (Halberg, 1959).

A rhythm (synonymous with oscillation, cycle) is defined by Minors and Waterhouse (1981) as " A sequence of events that repeat themselves through time in the same order and at the same interval." (p.2). This does not necessarily mean that a biological rhythm cannot change its characteristics. For example, under some circumstances certain biological rhythms may change their cycle length. Rhythms are usually typified by a number of

quantifiable characteristics. These include the period, the frequency, the amplitude, and the phase of the rhythm.

The period is the time taken to complete one cycle. Generally, the period is the basis for the classification of various rhythms. For instance, rhythms with a period of less than 24-hours are termed ultradian and rhythms with a period of more than 24-hours are termed infradian. Rhythms with a period of one year are called circannual rhythms.

The frequency of a rhythm is the reciprocal of its period. The frequency is the number of cycles within a given interval of time.

The amplitude of the rhythm can best be described with respect to a sinusoidal curve. The amplitude is the distance from the mean value to either extreme, the peak (maximum value) or the nadir (minimum value).

Rhythmic phase has several meanings. 'Phase' is defined by Conroy and Mills (1970) as " Any particular point in the cycle" (p.3). For instance the minimum point of the rhythm. The phase of the rhythm indicates the position of the rhythm in time. The rhythm is then said to be phase-shifted. The rhythm can further be described as being phase-advanced or phase-delayed. This describes the direction of displacement in time (Minors and Waterhouse, 1981). For instance following transmeridian flight in an eastward direction circadian rhythms often shift to an earlier phase position. Such rhythms are said to be phase-advanced. When flight is in a westward direction rhythms tend to shift to a later phase position. These rhythms are said to be phase-delayed.

The term 'phase' can also be used to describe the temporal relationship between two rhythms. Rhythms can be described as being 'in' or 'out' of phase with each other. For example, if the rhythm of body temperature is described as being 'in' phase with the rhythm of activity this means that similar aspects of the rhythm (such as the nadir) occurred simultaneously. When two rhythms are 'in phase' with each other they are said to be synchronized.

Synchronization refers to a steady state in which different rhythms run with the same period. When two rhythms are 'out of phase' they are said to be desynchronized and run with different periods. When the desynchronization is between an internal biological rhythm and an external event (such as the temperature rhythm and the day-night cycle, respectively) external desynchronization is said to exist. When the desynchronization is between two biological rhythms within the same organism (such as the temperature and cortisol rhythms) internal desynchronization is demonstrated.

Similarly, biological rhythms themselves can be internal (endogenous) or external (exogenous). Exogenous rhythms are those driven by external influences and are dependent upon an external timing source. For example, urinary volume is an exogenous rhythm because it is dependent upon the amount of fluid consumed. Exogenous rhythms cannot continue in the absence of environmental oscillation. Conversely, endogenous rhythms are driven by an internal timing mechanism which is sustained by the organism itself and does not depend upon an external time cue. Some examples of endogenous rhythms in the human circadian system include the temperature rhythm, potassium excretion, and cortisol secretion. Endogenous rhythms are said to be self-sustaining although they are often influenced by external events. A self-sustaining rhythm that is not influenced by any apparent environmental time cue which determines its period or frequency is called a free-running rhythm.

Free-running endogenous rhythms may die out after a few cycles or persist throughout an organisms lifetime. There is presumed to be some mechanism in the organism responsible for timing and controlling such rhythms. This mechanism is called an oscillator or pacemaker and is referred to by Brown and Graeber (1982) as " an inferred biochemical or cellular mechanism that generates an organismic rhythm, characterised by a feedback system guaranteeing a self-sustaining capacity." (p.463). This mechanism is often referred to metaphorically as the 'clock'. It has been postulated that human circadian system is composed of many clocks and that circadian organization is derived from the integrative relationships within this multioscillator system (Pittendrigh, 1960). While this position appears to have gained acceptance, the question arises as to whether control is exerted hierarchically by means of a 'master clock' (or primary circadian pacemaker).

The generation and maintenance of 'slave' (or secondary) oscillators is presumed to be one of the major functions of these primary oscillators.

Although rhythms are usually controlled endogenously, endogenous control and exogenous control commonly interact. Just as a clock seldom keeps perfect time and has to be periodically adjusted, so an endogenous rhythm may be constantly adjusted by some factor in the environment. It has been confirmed that for most animal species for whom circadian rhythms are allowed to free-run, the inherent period of the clock controlling the endogenous rhythm is not exactly 24-hours. When human beings are placed in isolation chambers their free-running rhythms are usually shown to be closer to 25-hours (Minors and Waterhouse, 1981). Rhythmic environmental influences such as the day-night cycle keep the biological clock synchronized to a 24-hour period. This process of synchronization of the endogenous clock to external influences is termed entrainment.

Any rhythm which exhibits a 24-hour period as a result of the daily alternation of light and dark is said to be entrained to the day-night cycle. Every rhythm has an upper and lower limit within which it can become entrained. This is termed the range of entrainment. This can be demonstrated experimentally by studying the rhythm under free-running conditions and applying artificial light cycles at various phases of the rhythm.

The external influences which are capable of entraining rhythms are referred to as zeitgebers or 'synchronizers' (Minors and Waterhouse, 1981). Only a few environmental variables are capable of entraining circadian rhythms in living organisms. Light is generally considered to be a principal zeitgeber although the ability of light to entrain human biological rhythms has been questioned. This issue is examined in the following chapter.

CHAPTER THREE: THE ROLE OF LIGHT IN BIOLOGICAL RHYTHMS

The capacity of the day-night cycle to entrain biological rhythms has been investigated in a wide variety of organisms. For most organisms this cycle acts as a zeitgeber which synchronizes endogenous rhythms with a free-running period of about 25-hours to the 24-hour solar day. Stable entrainment is achieved by repeated adjustments of period and phase.

The purpose of this chapter is to determine the capacity of light in entraining the human circadian system. The sensitivity of the human circadian system to light, the physiological structures which mediate the effects of light on the circadian system, and the therapeutic implications of light for depression will be discussed within this context.

Zeitgeber Properties of Light

Light has been demonstrated to be an effective entraining agent for most animal species. Investigations of free-running rhythms in animals indicate that shifts in the steady-state phase of these rhythms can be brought about by single pulses of light (Takahashi and Zatz, 1982). Studies of the zeitgeber properties of light in humans have produced varying results regarding the effectiveness of light as an entraining agent. Clearly, closer consideration of these findings is required.

Czeisler, Richardson, Zimmerman, Moore-Ede and Weitzman (1981) found that subjects demonstrated free-running rhythms close to 25-hours when exposed to an environment free from periodic time cues. However, when a light-dark cycle was imposed free-running rhythms such as body temperature and the sleep-wake rhythm became synchronized with the environmental cycle. When the light-dark cycle was removed subjects again demonstrated free-running rhythms.

The entrainment properties of light have also been demonstrated in studies of urinary excretory rhythms. Lobban (1967,1977) studied these rhythms in Indians and Eskimos living in Arctic regions where days are short and nights are long. Results showed that subjects' rhythms were of lower

amplitude and more irregularly phased than the excretory rhythms of control subjects living in non-polar regions or of visitors on holiday in this area.

Further evidence that light is implicated in entrainment comes from studies of blind individuals. Studies of cortisol rhythms (Krieger and Rizzo, 1971) and urinary excretory rhythms (Lobban and Tredre, 1964) in blind subjects show that the amplitude of these rhythms were reduced and their timing was more erratic than those of sighted controls. Along similar lines, Miles, Raynal and Wilson (1977) found rhythms of body temperature, performance, cortisol secretion, and urinary excretion which were desynchronized from the 24-hour day in a congenitally blind man. Instead, his rhythms free-ran with a period of 24.9 hours.

In contrast, some researchers have argued that light has a 'weak' effect in entraining the human circadian system. Wever (1979) reached this conclusion based on a number of findings. Aschoff (1979) and Wever (1979) found that some subjects isolated from time-free cues had rhythms that were free-running even in the presence of a light-dark cycle.

Furthermore, Wever maintained that acoustic signals were more effective zeitgebers than the light-dark cycle. In his (1970) experiment acoustic sounds or 'gong' signals were sounded at three hour intervals to signal and\or awaken subjects for periodic urine collections. Subjects were isolated from time-free cues apart from an overhead light-dark cycle. When the periodic signals were omitted the imposed light cycle was insufficient to entrain the subject to the 24-hour day. Entrainment occurred only when the light cycle and the gong signals were paired. The gong signal was interpreted as a personal call from the experimenter and therefore a 'social contact'. It was concluded that the gong signal was a powerful zeitgeber and the light-dark cycle had only a 'weak' effect.

However, arguments for the 'weak' effects of light suffer from interpretive problems. Subjects in Aschoff's (1979) and Wever's (1979) studies were permitted to use auxiliary lighting at 'night'. This means that subjects could effectively implement their own light regimen, provided they were prepared to sleep in the light. Under these circumstances subjects would exhibit free-running rhythms even in the presence of a light-dark cycle.

Moreover, serious doubts regarding the validity of the conclusions reached by Wever (1970) can be raised in view of the fact that the efficacy of the gong signal alone was never evaluated. A far more plausible explanation for the results is that the regular gong signals acted as an alarm clock. This would interrupt the subjects' sleep each morning, thereby facilitating adaptation to the imposed cycle of overhead lighting (Czeisler et al., 1981).

Direct versus Indirect Effects of Light

Those who have taken the position that light has a minimal effect on the human circadian system have traditionally argued that the light-dark cycle does not affect circadian rhythms via direct physiological action. It is suggested that any effects are the result of a behavioural reaction released indirectly by the alternation of light and dark.

Although this position has received some empirical support, (for example Wever, 1981) these studies have generally exposed subjects to light cycles with intensities of not more than a few hundred lux. Recent research appears to indicate that various intensities of light differentially affect the human circadian system and that, physiologically, the light intensities used in most experiments are too low to have any direct action. However bright light, of similar intensity to sunlight (>2000 lux), seems to have a biologically active entrainment effect. There is a growing body of research to suggest that bright light has a direct effect on the circadian system.

Bright versus Dim Light

Bright light appears to have an effect on the human circadian system that is qualitatively different to that of dim light. Wever, Polasek and Wildgruber (1983) found that bright light (4000 lux) increased the range of entrainment of human circadian rhythms under temporal isolation whereas dim light (<100 lux) did not. Czeisler, Allan, Strogatz, Ronda, Sanchez, Rios, Freitag, Richardson and Kronauer (1986) found that bright light produced phase-delays of the body temperature rhythm when applied to a certain phase of the rhythm. Honma, Honma, and Wada (1987) applied artificial bright light cycles (5000 lux) to two subjects in a temporal isolation unit with free-running sleep-wakefulness and temperature rhythms. Their findings

show that the bright light cycles successfully entrained these circadian rhythms.

Further support for the differential effects of bright and dim light on circadian rhythms comes from studies of the melatonin rhythm. Melatonin is a hormone which is typically found in low concentrations during the day, gradually rising during the night, peaking and returning to low levels during the morning hours. Lewy, Wehr, Goodwin, Newsome and Markey (1980) found that bright artificial light (2500 lux) suppressed nocturnal melatonin secretion in humans while light of ordinary room intensity (500 lux), shown to suppress melatonin secretion in other mammals, failed to do so.

A Physiological Pathway for Light

Animal studies have demonstrated the existence of a physiological pathway mediating the entrainment effects of light. Studies have generally shown anatomical connections between the photoreceptors and the circadian pacemaker. It has been difficult to investigate whether analogous structures exist in humans because of ethical problems. However, studies of humans following surgical removal of such structures due to tumors appear to suggest that the circadian anatomy of humans is similar (Moore-Ede, 1981). In view of this evidence it is important to consider findings from animal studies in terms of the specific structures which appear to mediate the effects of light.

Intensive investigations have enabled researchers to isolate the components of the system responsible for entrainment in most animals. As noted by Takahashi and Zatz (1982), three main components have been identified :

1. An input pathway for entrainment;
2. A circadian pacemaker that generates rhythmicity;
3. An output pathway resulting in the overt expression of the rhythm.

For photic entrainment to occur, a photoreceptor must be coupled to an input pathway. For it to be apparent it must be coupled to an output pathway. In mammals the photoreceptors responsible for entrainment are

located in the retina. Moore and Lenn (1972) found that a bilateral retinal projection terminated exclusively in the suprachiasmatic nucleus of the hypothalamus. The existence of this structure, known as the retinohypothalamic tract, has been well established in most vertebrate species (Moore, 1973). The conveyance of photic information along this tract has been substantiated by experiments in which the terminal nuclei of this projection were lesioned, resulting in abolition of some circadian rhythms (Rusak and Boulos, 1981). Lesions of the suprachiasmatic nuclei in experimental rats resulted in disruptions of wheel-running activity as well as the sleep, drinking, feeding, and temperature rhythms (Takahashi and Zatz, 1982). At present, there is no evidence of regrowth of retinohypothalamic fibers into areas adjacent to the suprachiasmatic nuclei after such lesions (Mosko and Moore, 1979).

Pathways other than the retinohypothalamic tract appear to mediate the synchronization of behaviour and physiology. Research suggests that photic entrainment may also involve the bilateral projection originating in the lateral geniculate nuclei and terminating in the suprachiasmatic nuclei (Roelfsema, 1987; Swanson, Cowan and Jones, 1974). Thus it appears that light impinging upon the retina reaches the suprachiasmatic nucleus via a multisynaptic pathway.

In vitro and in vivo studies have demonstrated the self-sustaining rhythmicity of the suprachiasmatic nuclei but not other parts of the brain (Roelfsema, 1987). The suprachiasmatic nuclei appear to have all the properties of an endogenous clock. Data from studies of rats with suprachiasmatic nuclei ablation show daily rhythms with abnormal amplitude or phase. These effects have been shown for a number of rhythms including corticosterone secretion (Szafarczyk, Ixart, Malaval, Nouguier-Soule and Assenmacher, 1979) and feeding (Abe, Kroning, Greer and Critchlow, 1979). Findings by Rusak and Groos (1982) indicate that electrical stimulation of the suprachiasmatic nuclei can cause either advance or delay shifts in some circadian rhythms.

Research findings strongly suggest that the suprachiasmatic nuclei are the basis of an endogenous oscillator. There is also compelling evidence for the presence of multiple circadian oscillators since some rhythms have been

found to persist following suprachiasmatic lesions. Such lesions were found to abolish the drinking rhythm in monkeys but not the temperature rhythm (Moore-Ede, Lydic, Czeisler, Fuller and Albers 1980, cited in Takahashi and Zatz, 1982). It appears that circadian oscillators located outside the suprachiasmatic nucleus may regulate various circadian rhythms. The location of these oscillators is as yet unknown.

Linking findings of animal studies to humans, Lydic, Schoene, Czeisler, and Moore-Ede (1980) found diffuse groups of neurons in human brains situated lateral to the third ventricle and above the optic chiasma. Some scientists believe these diffuse structures to be the suprachiasmatic nuclei. Thus the anatomical circadian system in humans may be comparable to that of other animals. Research findings that humans with retinal damage have irregular circadian rhythms which may free-run is consistent with the view that there is a physiological pathway linking the retina with a primary circadian pacemaker (for example, Miles et al., 1977).

Phototherapy

The entrainment effects of bright light on the human circadian system and a possible anatomical pathway through which these effects may occur, have important implications for the therapeutic role of light. In recent years light has been used to relieve depressive symptoms in some individuals with affective disorder. Phototherapy involves exposing depressed people to bright white light, of similar intensity to sunlight (> 2000 lux), for a few hours each day. The light source is covered by a plastic diffusing screen which absorbs ultraviolet light. Patients are usually seated facing the light at a fixed distance from the source so that light intensity is constant. During exposures patients are not required to look directly at the light but must keep their eyes open.

The duration and timing of exposures administered varies according to the particular theoretical position taken (see Chapter Five). Phototherapy is based on the general premise that overt disturbances in circadian rhythms reflect functional disturbances in the circadian system, such as abnormalities in the timing of the circadian pacemaker, which may be pathogenic for depression. Bright light may act via a physiological pathway similar to that

of other animals to correct the underlying disturbances. This, in turn, corrects the overt circadian rhythms and ameliorates depressive symptoms.

There is a growing body of research to suggest that phototherapy is an effective treatment for depressives exhibiting circadian rhythm disturbances. This evidence will be considered in Chapter Six.

Summary

Research has generally supported light as being an effective entraining agent in humans. Some researchers have argued that entrainment is indirect and is the result of behavioural reactions to light-dark alternations. However, studies which support this position have used only dim light exposures. In contrast, other research findings show that bright light has the capacity to directly entrain a variety of human biological rhythms.

Findings from animal studies indicate that direct entrainment is achieved through physiological connections from the retina to the suprachiasmatic nuclei via the retinohypothalamic tract and the geniculate nuclei. There is preliminary evidence to suggest that the suprachiasmatic nuclei exist in humans.

Phototherapy is a potential treatment for relieving depressive symptoms in some types of depression. Bright light is suggested to have a direct physiological effect upon disturbances in the circadian system thus correcting abnormal circadian rhythms and resulting in the amelioration of depressive symptoms.

CHAPTER FOUR: DEPRESSION AND CIRCADIAN RHYTHM ABNORMALITIES

Investigations of human circadian rhythms show that both endogenous and exogenous rhythms are synchronized to the light-dark cycle. Although this is apparent for healthy human beings, certain subgroups of the psychiatric patient population exhibit rhythms which appear to be desynchronized.

Special attention has been paid to rhythm disturbances in depression. Various subgroups of individuals diagnosed as depressed appear to have biological abnormalities within a number of circadian systems. Some of these individuals are severely depressed and require hospitalization. Phototherapy has been found to produce few side effects (headaches in some light-sensitive patients) and may be a useful non-pharmacological treatment for some types of depression.

The purpose of this chapter is to examine the characteristics of those subgroups of depressives who appear to demonstrate circadian rhythm disturbances and therefore may be appropriate candidates for phototherapy. The evidence for specific rhythm disturbances in these individuals is also considered.

Features of Depressed Subgroups

Within the category of depressive disorders there are two subgroups of individuals whose circadian systems deserve some investigation. One group is typically categorized as having endogenous depression. This type of depression is thought to result from disturbed physiological or biochemical processes. Those with endogenous depression are usually diagnosed as having Major Depressive Disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) (American Psychiatric Association, 1980) or Unipolar Disorder according to the Research Diagnostic Criteria of Spitzer, Endicott and Robins (1978). They may display symptoms such as anhedonia, low mood, weight change, and loss of energy. In addition, individuals who are considered to be endogenously depressed typically exhibit features of the DSM-III diagnosis for Melancholia. Melancholic symptoms include a loss of pleasure in almost all activities, lack of response to usually pleasurable

events, and early morning wakening. Other symptoms may include worsening of mood in the morning followed by improvement in the evening, marked psychomotor agitation or retardation, significant weight loss, and excessive or inappropriate guilt.

In contrast to other types of depression, endogenous episodes do not appear to be caused by a stressful life event. Although the biological processes responsible for endogenous depression are not yet well understood, the biological systems of these depressives are markedly impaired compared to those of healthy individuals.

A second group of individuals have been identified as having a disorder which also appears to have a biological component. This syndrome has been termed Seasonal Affective Disorder (SAD) (Rosenthal, Sack, Gillin, Lewy, Goodwin, Davenport, Mueller, Newsome and Wehr, 1984). The main features of this syndrome include characteristics of depression during the winter (such as decreased activity, low mood, carbohydrate craving, weight gain, oversleeping, decreased libido, and change in the quality of sleep). During the summer these depressive symptoms remit and in some cases are replaced by characteristics of hypomania including increased activity, elation, and weight loss.

In order to be considered within the SAD category individuals must meet the following criteria (Rosenthal et al., 1984):

1. A history of Major Affective Disorder;

2. Regularly occurring autumn-winter depressions (for at least two consecutive winters) which remit during spring or summer;

3. Absence of any other major psychiatric disorder;

4. Absence of any seasonally changing psychosocial variables to account for the changes in affect.

In addition, reported mood change with a change in latitude (mood improvement on nearing the equator) would strengthen the diagnosis.

Demographic data from two major studies of individuals with SAD (Rosenthal et al., 1984, Rosenthal, Sack, James, Parry, Mendleson, Tamarkin and Wehr, 1985a) reveal that the majority are classified as having Bipolar Affective Disorder according to the Research Diagnostic Criteria. A small number (about 10%) are classified as having Unipolar Disorder. Rosenthal et al. (1985a) found that 70% of individuals with SAD have at least one first degree relative with Major Affective Disorder and 38% had one first degree relative with SAD. SAD was also found to be more prevalent among women than men (4:1).

Endogenous depression and SAD appear to have biological concomitants. Several features of these disorders have been cited as evidence for circadian disturbances. These include time of awakening, daily variation in mood, the cyclicity of these disorders, and seasonal occurrences of affective disorders.

Time of Awakening

Early morning awakening is a well established feature of endogenous depression. This symptom may indicate that a component of the circadian system is abnormally advanced relative to other components of the sleep-wake cycle (Wehr, 1982). However, 64% of individuals with SAD were found to exhibit later times of waking during their winter depressive episodes (Rosenthal et al., 1985a). This may suggest that aspects of the biological rhythms of SAD individuals may be phase-delayed with respect to the sleep-wake cycle.

Daily Variation in Mood

Typically, endogenous depression is worse soon after waking with slight or even marked improvement in the afternoon or evening. This pattern tends to disappear as the depression becomes very severe, and frequently reappears during clinical improvement (von Zerssen, 1983). Individuals with SAD have not been reported to show this diurnal variation in mood.

Cyclicity of Depression

The recurrent nature of depression and mania is itself a kind of biological rhythm. Some endogenous depressives have depressive episodes followed by euthymic states which may cycle rapidly during the course of the illness. The occurrence of depressive episodes followed by a euthymic state or hypomania in SAD is therefore a type of biological (circannual) rhythm.

Seasonal Incidence of Affective Disorders

Episodes of depression in Major Depressive Disorder have been noted across all seasons although the number of admissions usually peak during the spring (Eastwood and Stiasny, 1978; von Zerssen, 1983). Episodes of mania in Bipolar Affective Disorder also occur more frequently during the spring (Mayer-Gross, Slater and Roth, 1969; Symonds and Williams, 1976). There is a clear seasonal pattern of regularly occurring depressions during the winter in SAD followed by remission in the summer (Rosenthal et al., 1984, 1985a).

These observations elucidate the fundamental differences between endogenous depression and SAD. Of particular importance is the finding that endogenous depressives appear to have less seasonal variation in symptomatology while those exhibiting symptoms of SAD (seasonal depressives) show clear seasonal changes. Based on such observations one would expect greater annual fluctuation in the rhythms of seasonal depressives. Specific circadian disturbances in both types of depression deserve special consideration.

Circadian Disturbances in Endogenous Depressives

There is a vast body of evidence to suggest disturbances in a number of rhythm parameters in endogenous depression. Abnormalities have been noted in the sleep-wake rhythm, the Rapid Eye Movement (REM) Sleep circadian rhythm, the temperature rhythm, the cortisol rhythm, and the melatonin rhythm. Although there is some variation across subjects, some generalizations can be made with respect to research findings in this area.

The aim here is not to present an exhaustive review of these studies but to consider general findings with respect to the types of circadian abnormalities which have been observed in endogenous depression.

Sleep-Wake Cycle

Von Zerssen (1983) notes that the sleep-wake cycle is altered in endogenous depression. In addition to repeated clinical observations of early morning awakening and diurnal variation in mood, some researchers have observed temporal disorganization in sleep architecture. Kupfer, Foster, Coble, McPartland and Ulrich (1978) found a reduction in slow wave (delta) sleep time and delta wave density. Other evidence is provided by studies of sleep deprivation. One night's total sleep deprivation has been reported to induce transient remissions, usually of one day's duration, in depression (Pflug and Tolle, 1971). Partial sleep deprivation in the second half of the night has been shown to be equally effective (Shiligen and Tolle, 1980). Also, switches into depression appear to take place during sleep (Doerr, von Zerssen, Fischler and Schulz, 1979).

REM-Sleep Circadian Rhythm

In normal individuals the distribution of REM-sleep is skewed with more REM-sleep occurring towards the end of the night (Dement and Kleitman, 1957). Maron, Rechtschaffen and Wolpert (1964) noted that the propensity to have REM-sleep is governed by a process that exhibits a rhythm independent of sleep.

Findings of REM-sleep studies have been extensively replicated. In general, studies appear to agree that:

1. Individuals exhibiting features of endogenous depression have more REM-sleep in the first third of the night than normal controls (for example, Gresham, Agnew and Williams, 1965; Kupfer et al., 1978, Kupfer, Shaw, Ulrich, Coble and Spiker, 1982) thus altering the distribution of REM-sleep time and activity from the normal pattern.

2. REM-sleep tends to occur earlier than usual thus reducing REM latency, the time elapsed from the onset of sleep to the first REM episode (for example, Beersma, van den Hoofdakker and van Berkestijn, 1983; Kupfer, 1976; Kupfer et al., 1978,1982; Schulz and Lund, 1983).

3. The first REM episode in depressed subjects is often prolonged compared to normal subjects (for example, Vogel, Vogel, McAbbee and Thurmond, 1980; von Zerssen, 1983).

Unfortunately, results are not as clear in studies of the temperature rhythm in endogenous depression.

Temperature Circadian Rhythm

Body temperature in normal subjects has been found to follow a characteristic pattern which is low on waking and rises rapidly until about mid-morning. It then remains fairly stable until the evening where it reaches its maximum around midnight and then falls to a minimum value around 0400 hours (Minors and Waterhouse, 1981).

Numerous studies of temperature rhythms in endogenous depression have been conducted. One should also bear in mind that most studies of temperature rhythms in depression are subject to a number of criticisms. These include the use of subjects on medication, failure to monitor temperature continuously over a 24-hour period, and measurement of oral temperature which is far more variable than rectal temperature. With these

limitations in mind, most studies in this area do appear to agree on certain points:

1. Temperature during sleep is higher in depression compared with recovery or with normal subjects (for example, Avery, Wildschiodtz and Rafaelson, 1982; Schulz and Lund, 1983; Wehr, Muscettola and Goodwin, 1980).

2. The phase position of the temperature circadian rhythm may be abnormally early in endogenous depression (for example, Cahn, Folk and Huston, 1968; Kramer and Katz, 1978; Wehr et al., 1980; Lee and Taylor, 1983).

3. Temperature circadian disturbances appear to be partly state dependent, that is the rhythm becomes more nearly normal upon recovery (for example, Avery et al., 1982; Kramer and Katz, 1978; Pflug, Erikson and Johnsson, 1976).

Cortisol Secretory Rhythm

Like the temperature rhythm, the cortisol rhythm has been extensively investigated in humans. Wehr (1982) notes that in normal individuals cortisol is secreted in pulsatile bursts seven to nine times a day. During the first portion of sleep no secretory episodes occur. A few hours after sleep onset one or two low-level bursts occur followed by a sharp rise of cortisol levels around mid-sleep, reaching a maximum around the time of waking.

Many of the criticisms made of temperature rhythm studies also apply to studies of cortisol. In addition, some studies in this area have not exposed subjects and controls to the same environment. Others have failed to control for age which, as Halbreich (1984) notes, has been shown to contribute to increased cortisol levels. Despite these shortcomings most studies of cortisol secretion in endogenous depression agree that:

1. Mean cortisol secretion is higher in endogenous depression than in normal controls (for example, Beck-Friis, Kjellman, Aperia, Unden, von Rosen, Ljunggren and Wetterberg, 1985a; Fullerton, Wenzel,

Lohrenz and Fahs, 1968; Knapp, Keane and Wright, 1967; Sachar, Hellman, Roffwarg, Halpern, Fukushima and Gallagher, 1973).

2. The phase position of the cortisol secretory rhythm is advanced in endogenous depression (for example, Doig, Mummery, Wills and Elkes, 1966; Knapp et al., 1967; Fullerton et al., 1968; Sachar et al., 1973; Yamaguchi, Maeda and Kuromaru 1978, cited in Wehr, 1982).

3. On recovery from depression, cortisol levels and shifts of the cortisol rhythm become more nearly normal (for example, Beck-Friis et al., 1985a; Doig et al., 1966).

4. There is a greater likelihood that depressed people will show an abnormal response to the Dexamethasone Suppression Test (DST). That is there is a failure to suppress cortisol below 200 nmol/L after dexamethasone is administered, in endogenous depression (for example, Beck-Friis et al., 1985a; Lee and Taylor, 1983; Wetterberg, 1983).

The circadian rhythms of REM-sleep, temperature, and cortisol are closely linked. Studies of free-running normal subjects reveal that REM-sleep propensity is maximal just after the body temperature minimum (Czeisler, Zimmerman, Ronda, Moore-Ede and Weitzman 1980; Zulley, 1980). Usually, the temperature minimum occurs in the latter half of the sleep period and REM-sleep becomes maximal near dawn, around the time of the daily cortisol maximum.

The close association between these rhythms suggests that they may be controlled by the same oscillator (Wehr, 1982). If this is the case one might expect that an abnormality in one system would be accompanied by corresponding changes in the other rhythms. Unfortunately, studies examining these rhythms simultaneously in people with depressive symptoms are lacking.

Melatonin Circadian Rhythm

Melatonin is normally found in the body in low concentrations during daylight hours. The level gradually rises during the evening and reaches a

peak around midnight, then falls rapidly and returns to low levels during the early morning hours (Lewy et al., 1980).

The melatonin rhythm is of particular interest because it is suggested to have a pathological role and is thought to result in the expression of depressive symptoms. In view of the hypothesized nature of this rhythm the findings of individual studies on melatonin in endogenous depression will be considered in some detail.

The first study of the melatonin rhythm in depression was conducted by Wetterberg, Beck-Friis, Aperia and Petterson (1979) in which a depressed 48-year old woman was reported to have low melatonin levels, even during the nocturnal phase. They also found that the peak melatonin concentration was phase-advanced during the depressive episode compared to recovery.

This finding of lower nocturnal melatonin levels in endogenous depression has been well replicated. Wirz-Justice and Arendt (1979) found lower melatonin levels in six unipolar depressives at 0800 hours(h) compared with twelve healthy subjects. Mendlewicz, Linkowski, Branchey, Weinberg, Weitzman and Branchey (1979) found an absence of the normal nocturnal increase in three of four depressed patients compared with that measured in five normal subjects. In a summary of an experimental series by his group, Wetterberg (1983) reported lower serum melatonin levels at 0200h in 17 endogenous depressives compared to 22 healthy subjects and 15 non-endogenous depressives. In addition, only endogenous depressives showed non-suppression of cortisol in response to dexamethasone in the DST.

Brown, Kocsis, Caroff, Amsterdam, Winokur, Stokes and Frazer (1985) found lower nocturnal concentrations of melatonin in seven male endogenous depressives compared to five healthy male controls and nine non-endogenous female depressives. Similar findings are indicated by Beck-Friis et al. (1985a) who reported significantly lower nocturnal melatonin levels in 17 depressives with abnormal DSTs compared to 24 depressives in remission and 33 healthy controls. The patients in remission and healthy subjects had normal responses to dexamethasone.

Linking findings of melatonin and cortisol rhythms, studies appear to agree that low melatonin in endogenous depression is related to high levels of cortisol and an abnormal DST (for example, Beck-Friis et al., 1985a; Beck-Friis, Ljunggren, Thoren, von Rosen, Kjellman and Wetterberg, 1985b; Wetterberg, Aperia and Beck-Friis, 1981). Some studies suggest a phase-advance of the melatonin rhythm in endogenous depression. However, this appears to be a less consistent finding.

Rhythm Disturbances in Seasonal Affective Disorder

Research to date clearly indicates disturbances in the rhythms of endogenous depressives. Unfortunately, the existing research on the rhythms of seasonal depressives is very limited, making comparisons difficult. Abnormalities have been found in the sleep-wake cycle, temperature, and melatonin rhythms.

Rosenthal et al. (1985a) found that of 125 individuals with SAD, 64% reported later waking and 80% slept longer during a winter depressive episode. Similar figures are reported in Rosenthal et al.'s (1984) study of 29 seasonal depressives. Of these subjects, 76% reported later waking and 97% slept longer. In addition, the results of EEG sleep studies on nine of these patients showed that total sleep time and sleep latency was significantly increased in winter compared with summer recordings. Delta sleep also decreased significantly although REM latency and REM density did not change.

Lewy, Sack and Singer (1985) measured rectal temperature in a subject diagnosed as having SAD. They found that the overnight temperature minimum occurred around 0500h which is slightly phase-delayed compared to normal subjects.

Rosenthal et al. (1984) compared summer-winter responses to the Dexamethasone Suppression Test in seven seasonal depressives. All showed normal cortisol suppression. Rosenthal et al. (1985a) found that only two out of twenty seasonal depressives failed to show normal cortisol suppression. The authors note that this low prevalence of abnormal DSTs (10%) is similar to that reported in normal populations.

Studies of the melatonin rhythm in SAD are few. Brown et al. (1985) showed that nine depressed patients who did not exhibit features of endogenous depression had melatonin levels that did not differ from those of normal subjects. Furthermore, Rosenthal et al. (1985a) note that these subjects resembled seasonal depressives, who do not display features of endogenous depression. These authors also report that the seasonal depressives they have studied have not exhibited reduced levels of melatonin.

Lewy, Sack, Miller and Hoban (1987) measured melatonin onset in eight SAD subjects, currently depressed, and seven normal controls. Average times of melatonin onset were significantly delayed in the depressives compared to the controls.

Interestingly, Beck-Friis, von Rosen, Kjellman, Ljunggren and Wetterberg (1984) found a longer duration of melatonin secretion in winter than in spring and summer in both depressives and normal controls. Similar results are reported by Illnerova, Zvolsky and Vanecek (1985) for healthy urbanized subjects. It is not yet known whether the secretory profiles of melatonin differ between summer and winter in SAD (Rosenthal et al., 1985a).

Studies of rhythms in seasonal depression require further confirmation before definite statements can be made regarding specific rhythm disturbances. Preliminary evidence, however, does appear to suggest that the rhythms of these individuals are phase-delayed.

Light, Mood and Rhythms

Recent studies of depressives show that bright light has the capacity to shift disturbed circadian rhythms to a phase position similar to that of healthy subjects.

Dietzel, Saletu, Lesh, Sieghart, and Schjerve (1986) found that following seven non-consecutive hours exposure to bright light the plasma cortisol, REM-sleep, and temperature rhythms in ten endogenous depressives shifted towards phase positions similar to those of ten normal controls. Futhermore, mood was significantly lower compared to the controls before but not after bright light.

Lewy et al. (1987) found that the melatonin rhythms of eight seasonal depressives were significantly phase-delayed compared to normal controls prior to but not after a week of bright light exposure in the morning. In addition, patients were no longer significantly depressed compared to controls following this exposure.

These findings have been taken as evidence for the ability of bright light to correct circadian phase position and for its corresponding antidepressant action. Further findings in this area will be presented in Chapter Six.

Summary

Exposure to bright light is thought to be effective in reducing symptoms of depression in individuals with disturbed circadian rhythms. Two groups of individuals exhibiting depressive symptoms are of interest: Endogenous depressives and individuals with Seasonal Affective Disorder.

Both types of depressives appear to display abnormalities of various circadian systems. Endogenous depressives seem to have an advance of the sleep-wake cycle (early morning wakening), are more likely to show diurnal variation in mood, and are more consistently depressed all year round. By contrast, seasonal depressives tend to have delayed sleep-wake cycles (later waking), do not show diurnal variation in mood, and become depressed during the winter followed by spring/summer remission.

Differences have also been noted in the REM-sleep cycle, temperature rhythm, and the melatonin rhythm. Generally, endogenous depressives have more REM-sleep in the first third of the night and reduced REM latency. They also show a phase-advance of the temperature, cortisol, and possibly melatonin rhythms. There are also higher temperatures and cortisol levels noted in endogenous depressives as well as low levels of nocturnal melatonin. Preliminary studies of seasonal depressives suggest a phase-delay of the temperature and melatonin rhythms, normal distribution of REM-sleep, and normal nocturnal concentrations of melatonin. Further research is needed to confirm findings of phase-delays in seasonal depressives.

Further differences have been noted in response to the Dexamethasone Suppression Test. Most endogenous depressives have abnormal DSTs whereas seasonal depressives have generally been found to have normal DSTs.

Bright light has been found to shift disturbed circadian rhythms to their correct phase positions and to produce a corresponding antidepressant effect in both endogenous and seasonal depressives.

CHAPTER FIVE: THEORIES OF THE ANTIDEPRESSANT ACTION OF LIGHT

Various theoretical positions for the antidepressant properties of light have been proposed. A number propose that inadequate exposure to light during a critical stimulatory photoperiod results in depression. Another suggests that depression arises when rhythms become desynchronized with respect to the sleep-wake cycle. Yet another hypothesizes that the melatonin rhythm has a direct role in mediating depressive symptoms.

The purpose of this chapter is to review and evaluate the theoretical positions which propose the various mechanisms by which phototherapy might work to relieve depression.

Theories of Photoperiodic Time Measurement

Theories concerning photoperiodic mechanisms come largely from work with plants and animals. The idea that photoperiodic time measurement is based on an endogenous circadian rhythm of photosensitivity was advanced by Bunning (1960). He proposed that the 24-hour period comprised two half cycles differing in their sensitivity to light. Organisms are insensitive to light during the first 12 hours or photophil (the "light-requiring" half cycle). They become sensitive to photic stimulation during the second 12 hours or scotophil (the "dark-requiring" half cycle). Short day (winter) effects are produced when light is restricted to the photophil. Long day (summer) effects occur when light extends into the scotophil.

Photoperiodic theory assumes that there is a critical stimulatory photoperiod which may vary in duration both between and within species. This critical photoperiod controls the seasonal responses of organisms according to the ratio of light and dark provided by the environment. The photoperiod is important for reproductive response since it determines whether an animal becomes and/or remains reproductively competent or whether it becomes infertile. More specifically, some animals breed only when light is restricted to the photophil (short day breeders) and the critical stimulatory photoperiod is not exceeded. Others breed only when light extends into the scotophil (long day breeders) when the critical

stimulatory photoperiod is exceeded. If these requirements are not met the animal becomes anoestrus/aspermatogenic.

With respect to animal reproduction, photoperiodic theory assumes that exposure to summer days for long day breeders and winter days for short day breeders leads to the release of hormones which promote and maintain gonadal growth. Melatonin is thought to have an important role in the seasonal responses of animals since it has been noted to stimulate gonadal activity in short day breeders and to inhibit such activity in long day breeders. Consequently, concentrations of melatonin are increased during winter in short day breeders and decreased during summer in long day breeders (Bittman, 1985). Melatonin is affected by seasonal changes in light intensity and duration. Melatonin secretion is suppressed by light (Lewy et al., 1980). Rosenthal et al. (1984) note that in every species studied the duration of melatonin secretion is longest in the winter (when the photoperiod is shortest) and shortest in the summer (when the photoperiod is longest).

Photoperiodic theory is the foundation for two models, the photoperiodic model of seasonal depression and the external coincidence model of endogenous depression. Both models stress the importance of the timing of light exposure in relieving depressive symptoms.

External Coincidence Model

Based on the photoperiodic responses of the hamster, Kripke, Risch, and Janowsky (1983a) proposed a mechanism by which inadequate light exposure might lead to disturbed biological rhythms in endogenous depressives. When the hamster, a long day breeder, is exposed to darkness during its critical photosensitive interval hormones such as prolactin and luteinizing hormone are reduced. As a result, the animal becomes less aggressive and sexually inactive - behavioural features resembling endogenous depression.

By way of analogy, it was hypothesized that endogenous depression occurs when humans are not exposed to adequate light during a critical photosensitive interval. Since advance shifts have been noted to occur in the rhythms of some depressives, it was also assumed that this critical interval

might occur in the early morning hours. This would mean that the critical stimulatory photoperiod would end too early before dawn leading to inadequate light stimulation.

The underlying assumption is that the failure to illuminate the critical photosensitive interval leads to the induction of "winter type" responses in humans, including biological changes which may result in depressive symptoms. Bright light exposure in the morning, around the individual's usual time of awakening, is expected to illuminate the sensitive part of the rhythm of photosensitivity thereby leading to relief from depressive symptoms.

This model, however, has some serious drawbacks. Kripke et al.'s (1983a) observation that endogenous depressives exhibit similar behaviours to hamsters during winter (less aggression and sexual inactivity) seems to be a weak basis for comparison. These features alone do not make up the depressive syndrome. Furthermore, not all humans that exhibit these features are depressed. The analogy between depressives and hamsters appears to be inappropriate especially since the winter responses of hamsters are the result of gonadal regression. There is no evidence to suggest that depressives are reproductively incompetent.

The external coincidence model shows weakness in the lack of specificity regarding the underlying biological changes leading to the expression of depressive symptoms. Kripke et al. (1983a) note that prolactin and luteinizing hormone are reduced in the hamster during winter, but they do not explain how these may affect the human circadian system and whether they have a causal role in depression.

Furthermore, this model does not explain why the rhythms of endogenous depressives might be phase advanced compared to healthy individuals but assumes this to be the case on the basis of prior research findings. Clearly, this model requires experimental support. Studies which test the predictions proposed by the external coincidence model will be considered in the following chapter.

Photoperiodic Model

Like the external coincidence model, the photoperiodic model of depression is based on the seasonal responses of animals to light. The photoperiodic model suggests that people with SAD, like other animals, have circadian rhythms which are particularly sensitive to changes in the length of the photoperiod. As day length shortens during winter light is restricted to the insensitive part of the rhythm of photosensitivity. This triggers the release of various hormones, including melatonin which is suggested to mediate depressive symptoms in SAD. Towards summer, day length increases and light extends into the sensitive part of the rhythm, resulting in decreased levels of melatonin and subsequent remission.

This model emphasizes the importance of the timing of light administrations relative to the circadian rhythm of photosensitivity in suppressing melatonin and relieving depressive symptoms. The photoperiodic model predicts that lengthening the winter photoperiod, so as to simulate a spring/summer photoperiod, will illuminate the sensitive part of the rhythm and produce an antidepressant effect. Although exposure to light before dawn and after dusk are the suggested times of administration, light given at either end of the day could conceivably extend the photoperiod so that the sensitive part of the rhythm is affected.

There appears to be some support for the photoperiodic model. Data from studies of SAD individuals are consistent with a pattern of regularly occurring depressive episodes during short photoperiods and remission during long photoperiods (Rosenthal et al., 1984, 1985a).

There is also evidence of neural connections from the retina to the site of melatonin synthesis. Studies of animal physiology show that retinal receptors are connected to the suprachiasmatic nuclei via the geniculate nuclei and retinohypothalamic tract. The suprachiasmatic nuclei relay fibers to the lateral hypothalamic nuclei which project to the columns of the spinal cord. Neurons here provide the connections to the superior cervical ganglia which innervate the pineal gland (Moore, 1978). The pineal gland is the principal site for melatonin synthesis. There is some evidence to suggest that similar connections to the pineal gland exist in humans (Kneisley, Moskowitz

and Lynch, 1978; Vaughnan, McDonald, Jordan, Allen, Bell and Stevents, 1979).

The photoperiodic model is also open to criticism on several grounds. One of its most serious limitations is the failure to explain why annual changes do not lead to deterioration of mood in all individuals but only SAD sufferers. In essence, the model does not explain why seasonal depressives should be more receptive to photoperiodic cues than other individuals.

Another problem is that the seasonal responses of SAD individuals may be influenced by psychological reactions to changes in weather. Although SAD patients are screened to ensure that their depressions are not the result of anniversary reactions (Rosenthal et al., 1984) these individuals may be more prone to "feel" depressed during bleak cold winter days, and better during warm sunny summer days. Phototherapy may bring about an antidepressant response by bringing hope of relief rather than actual biological change. This rival explanation is possible in many studies which have failed to control for a psychological reaction or placebo and will be addressed in the following chapter.

Finally, as the following discussion of the melatonin-suppression hypothesis shows, research on the role of melatonin in depression has generally not supported the notion that this hormone is responsible for depression.

Melatonin-Suppression Hypothesis

This hypothesis suggests that bright light relieves depressive symptoms by suppressing melatonin. Unlike the photoperiodic model which emphasizes the importance of the timing of light, this model stresses the importance of the intensity of exposure. It assumes that light of sufficient intensity to suppress melatonin secretion will relieve depression regardless of the time of administration. The duration of light exposure may also be an important factor.

As noted previously, there is some evidence to suggest connections between the retina, a primary pacemaker, and the main site of melatonin

synthesis. However, there is little research to support proposals that melatonin mediates depressive symptoms. Rosenthal et al. (1985a) administered melatonin orally to eight seasonal depressives while receiving morning and evening light, which was currently lowering depression ratings. Melatonin and placebo capsules were administered orally in order to prolong the nocturnal rise in melatonin. After a week of melatonin and light treatment, melatonin brought back some but not all of the depressive symptoms. However, many of the effects of phototherapy were not reversed and patients' state was still better overall on this schedule than they were before light treatment. The authors concluded that melatonin may have a partial role in mediating depressive symptoms. However, the following winter Rosenthal et al. (1985a) found that the administration of atenolol, a beta-adrenergic blocker that can reduce nocturnal melatonin, failed to significantly lower depression ratings in a group of seasonal depressives.

If melatonin was responsible for depression, one might expect that depressives would have high levels of melatonin and that light treatments would work by maintaining low levels in the body. However, there is some suggestion that non-endogenous (seasonal) depressives have normal levels of melatonin (Brown et al., 1985; Rosenthal et al., 1985a). Furthermore, endogenous depressives appear to have low nocturnal concentrations of melatonin (Brown et al., 1985; Wetterberg, 1983; Wirz-Justice and Arendt, 1979).

Some studies of melatonin have involved normal subjects. If melatonin was responsible for depressive symptoms, one would expect that melatonin administered to healthy controls would have some profound effects upon mood and behaviour. Lieberman, Garfield, Waldhauser, Lynch, and Wurtman (1985) administered melatonin to 14 healthy controls in a double-blind placebo-controlled cross-over study. Blood samples were taken hourly and melatonin was administered such that high levels would be maintained. Results indicated that fatigue and sleepiness were significantly increased but mood was not affected.

In a similar experiment Arendt, Bojkowsky, Folkard, Franey, Marks, Minors, Waterhouse, Wever, Wildgruber and Wright (1985) administered melatonin and a placebo to healthy subjects in two double-blind cross-over

studies. Twelve subjects were studied during spring for one month and eleven others were studied during autumn. In autumn, five of the eleven volunteers showed a clear one to three hour advance of the melatonin rhythm compared to two out of twelve in the spring experiment. No significant phase-shifts were noted in either season. Moreover, the cortisol rhythm remained unchanged in both seasons. There was a significant increase in fatigue but no other significant changes in sleep or mood were noted in either experiment.

In sum, hypotheses suggesting a direct role of melatonin in depression do not account for all the effects observed in depressives. The melatonin-suppression hypothesis lacks empirical support.

Phase Response Curve Model

Lewy, Sack, Frederikson, Reaves, Denny, and Zielske (1983) proposed a hypothetical phase response curve for humans and have used this as a basis for the treatment of sleep disorders. This model was later extended to explain how light could be used to ameliorate depression in some types of depressive disorder.

Lewy, Sack and Singer (1984,1985) hypothesize that a desynchronization between the sleep-wake cycle (or sleep-dependent process) and other circadian rhythms results in the manifestation of depression. Sleep in endogenous and seasonal depression is shifted but not as much as other circadian rhythms. Appropriately timed light exposure will shift circadian phase position and hence correct the desynchronization between sleep and other rhythms. The authors suggest that the phase response curve can be used to predict the times of exposure most likely to bring about an antidepressant effect.

This phase response curve is based on the responses of animals to the

day-night cycle. Takahashi and Zatz (1982) note that extensive research in this area shows that all animal species have a phase response curve with three main features:

1. Little or no phase-shift occur after light pulses given during the organisms 'subjective ' day (active half cycle);

2. Phase-delays after light pulses applied to the early portion of the organisms 'subjective' night (inactive half cycle);

3. Phase-advances occur after light pulses given during late 'subjective' night (early morning).

In other words, light exposure during the day will not affect an animals' rest-activity cycle. The closer to the early portion of subjective night, that is dusk, the light is given the more likely the rest-activity cycle is to be delayed. The closer to early morning, that is dawn, light occurs the more likely it will advance. Lewy et al. (1983) note that the magnitude of the phase-shifts decreases near subjective dawn and dusk. The size of the phase-shift increases near the middle of the night where there is an inflection point separating phase-advance from phase-delay (see Figure 1).

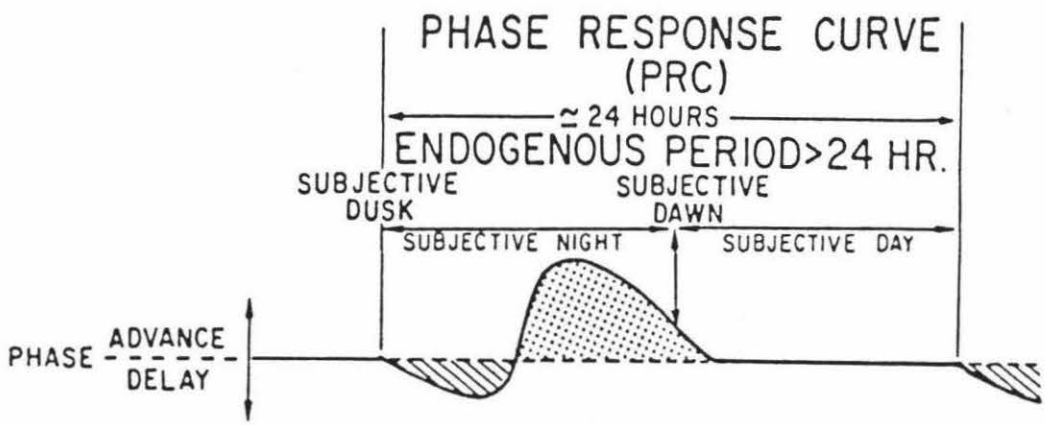

FIGURE 1: Hypothesized phase response curve for humans (and animals) with intrinsic periods of greater than 24-hours. From Lewy et al. (1983).

This model assumes that the human phase response curve is similar to the phase response curve of other animals whose endogenous periods are greater than 24-hours. Optimal times of light exposure are predicted according to the direction in which the rhythms are shifted. Sleep offset can be used to determine phase shifts. That is, endogenous depressives with early morning wakening (phase-advanced rhythms) should respond to bright light in the evening. This is expected to delay circadian phase position. In contrast, seasonal depressives with morning hypersomnia (phase-delayed rhythms) should respond to bright light in the early morning hours. This should advance circadian phase position. Endogenous and seasonal depressives are therefore considered to be biologically different and require different times of exposure in order to obtain the optimum antidepressant effect.

The efficacy of this model depends, to a large extent, upon the appropriateness of a phase response curve to light for humans. Until recently no research had been conducted in this area, probably because data collection is very time consuming. However, preliminary studies appear to show that bright light shifts circadian phase position in humans in a similar way to that noted in animals.

Lewy, Sack and Singer (1984) studied the responses of the melatonin rhythms in four normal volunteers to light pulses administered so as to shift circadian phase position. During summer (dawn at 0600h and dusk at 2100h) their nocturnal onset of melatonin production occurred at 2200h. Dusk was then advanced to 1600h for one week. At the end of this period melatonin onset had advanced a total of 2.5 hours compared to baseline. During the last week of the study dawn was delayed to 0900h. By the end of this week melatonin onset had delayed one hour.

Along similar lines, Lewy et al. (1984) report on a study of REM latency in 4 seasonal depressives. Subjects avoided bright light exposure after 1600h and slept between 2300h and 0600h. For one week dim light only was allowed between 0600h and 0900h. In the second week patients were exposed to 2000 lux of bright light during this time. REM latency was measured at the end of both weeks. REM latency was significantly shortened following the week of morning bright light but not after dim light. It appears that bright light advanced the circadian rhythm of REM sleep.

These findings support the existence of a human phase response curve with an advance portion in the morning and a delay portion in the evening. Other evidence consistent with this position comes from studies of rhythms following transmeridian flight.

Following travel across many time zones, the circadian system is in a state of desynchronization. Travellers usually experience shifts in a number of endogenous rhythms, become fatigued, and some experience transient lowering of mood (Roelfsema, 1987). It may take up to a week for rhythms to become resynchronized and return to their correct phase positions. For organisms with an endogenous period longer than 24-hours, the phase response curve suggests that resynchronization is faster following delay shifts than after advance shifts. This is consistent with the well replicated finding that, in humans, resynchronization is faster after west-bound flights, equivalent to a delay shift, than after east-bound flights, equivalent to an advance shift (Roelfsema, 1987).

Studies of the circadian rhythms of depressives are also consistent with Lewy et al.'s (1983) phase response curve that endogenous depressives have phase-advanced rhythms while seasonal depressives have delayed rhythms. In the previous chapter endogenous depressives were noted to have phase-advances of the sleep, temperature, cortisol, and possibly melatonin rhythms. Seasonal depressives have been shown to exhibit phase-delays of the temperature and melatonin rhythms.

This model, however, does not account for the finding that some individuals whose rhythms are desynchronized relative to the sleep-wake cycle as the result of experimental manipulations actually experience improvement in mood and performance (Wever, 1982). Furthermore, the phase response curve model does not explain all the rhythm disturbances in depression. For example, it does not account for the changes in cortisol and melatonin concentrations noted in endogenous depression. Moreover, further research is needed to confirm the existence of a phase response curve in humans. Nevertheless, the phase response curve model does make some seemingly valid and testable predictions regarding the optimal application of light in endogenous and seasonal depression. This model will be evaluated

more fully following consideration of findings of studies which test these predictions.

The Photon-Counting Hypothesis

The photon-counting hypothesis stresses that the timing of light is not critical for the antidepressant effect. It suggests that the duration of bright light exposure, that is the total number of photons, is important in relieving depressive symptoms.

This hypothesis, however, does not specifically state the length of exposure required to produce the antidepressant effect. Furthermore it fails to explain why the duration of light exposure is important and is therefore difficult to evaluate from a theoretical viewpoint. Proper evaluation of the photon-counting hypothesis requires examination of the research which supports or refutes this position. This evidence will be considered in the following chapter.

Summary

A number of theoretical positions suggest that bright light has the capacity to ameliorate depression in endogenous and seasonal individuals.

Theories differ as to how bright light is thought to bring about this effect. The external coincidence and photoperiodic models propose that depression occurs when humans are not exposed to adequate light during a critical photosensitive interval. The external coincidence model suggests that this critical interval, like other rhythms in endogenous depressives, is phase-advanced. Hence it occurs during the early morning hours when there is insufficient illumination. Light exposure during this interval is expected to relieve depression. By contrast, the photoperiodic model suggests that lengthening the winter photoperiod to simulate a spring/summer photoperiod will have a similar effect in seasonal depressives. This model emphasizes the timing of light in reducing melatonin, which is thought to be responsible for depressive symptoms.

The melatonin-suppression hypothesis also suggests that melatonin mediates depressive symptoms. However, this position stresses the importance of the intensity of bright light exposure in relieving depression. The duration of light may also be important in the suppression of melatonin hence this view is consistent with the photon-counting hypothesis which suggests that the total number of photons is critical for the antidepressant effect.

Lewy et al. (1985) propose that depression results from desynchronization of the sleep-wake cycle with other rhythms. Their phase response curve model suggests that early morning light exposure in seasonal depressives and early evening exposure in endogenous depressives will shift circadian phase position. This should bring about the resynchronization of rhythms, resulting in an improvement in mood.

Closer examination of these theoretical positions reveals a number of weaknesses. The photoperiodic and external coincidence models are among the least plausible explanations, their propositions being drawn from observations of animal behaviours which appear to have little applicability to humans. The melatonin-suppression hypothesis has generally not been supported by the research and seems unlikely since depressives have generally not demonstrated abnormally high levels of melatonin. Also, the photon-counting hypothesis requires verification from research findings.

The phase response curve model appears to be the most plausible explanation for the antidepressant effect of light. Preliminary findings suggest that the animal model on which this is based may be applicable to humans.

All theoretical positions require rigorous testing according to the light schedules proposed to be effective. The next chapter reviews some of the studies of phototherapy and evaluates the theories more fully in the light of research findings.

CHAPTER SIX : PHOTOTHERAPY RESEARCH IN DEPRESSIVES : FINDINGS AND METHODOLOGICAL CONSIDERATIONS

There is a rapidly growing body of research which examines the effectiveness of phototherapy in reducing depressive symptoms. Researchers have used various experimental schedules to test the different theoretical positions. These have included the use of light to lengthen the photoperiod (photoperiodic model); light exposure in the morning (external coincidence model); morning light exposure for seasonal depressives (phase response curve model); and specific durations (photon-counting hypothesis) and intensities (melatonin-suppression hypothesis) of light regardless of the time of exposure.

This chapter will critically examine the research findings for phototherapy as a potential treatment modality for depression and attempt to determine the validity of these findings. The research will also be discussed in terms of support for the theoretical positions presented in the previous chapter.

Studies of Photoperiodic Models

Lewy, Kern, Rosenthal, and Wehr (1982) exposed a 63 year old male, diagnosed as having Bipolar Disorder according to the Research Diagnostic Criteria, to bright light. The subject, currently 16 weeks into a winter depressive episode, was administered 2000 lux of bright fluorescent light from 0600h to 0900h and 1600h to 1900h daily. Mood was evaluated by self-ratings and observer (nurses) ratings of depression, and 24-hour activity counts. After ten consecutive days' exposure to bright light, self-ratings of mood and activity counts increased while nurses ratings of depression decreased. It was concluded that the patient switched out of his depression as a result of exposure to a spring photoperiod.

This study, however, has some major limitations since it involved only a single subject and lacked a control group. Also, there is no indication that the observers were blind to the treatment and consequently the results may have been biased. Furthermore, depressive episodes appear to be time limited thus spontaneous remission may have occurred.

Other studies have tested the photoperiodic model using subjects as their own controls. Rosenthal et al. (1984) exposed nine bipolar (eight female, one male) seasonal depressives to both bright (2500 lux) and dim (100 lux) light for three hours before dawn and three hours after dusk. Treatments were administered using a counterbalanced cross-over design. Subjects self-administered the light treatments in their own homes. Following random assignment to treatment conditions, subjects were exposed to either bright or dim light for one week. During the third week subjects received the other light treatment. The second and fourth weeks were withdrawal conditions in which subjects received neither treatment. Self-report (Beck Depression Inventory) and observer (Hamilton Rating Scale) measures of depression were administered at the end of each week. Bright light was found to reduce depression ratings whereas dim light did not show a significant effect. Mood improvement occurred within a few days of beginning bright light treatment. Relapse occurred within a similar time period following termination of light treatment.

In a partial replication of this study, Rosenthal, Sack, Carpenter, Parry, Mendelson and Wehr (1985b) exposed seven outpatient and six inpatient seasonal depressives to light using the same procedure. Inpatients received light treatment in a hospital environment while outpatients were responsible for their own light administrations. The dim light intensity was 300 lux for outpatients, 5 lux for inpatients and the bright light intensity was 2500 lux for both groups. On completion of the study bright light only was administered to 11 patients in the evening hours. Results showed a significant decrease in depression scores on the Hamilton Rating Scale for both outpatients and inpatients following bright light treatment. No such effect resulted after dim light. Mood improved within two to four days of beginning bright light and deteriorated after withdrawal.

Seven of the eleven subjects exposed to bright light in the evening showed some response (defined as a decrease in Hamilton ratings by four points or more). It is not reported whether these changes were significant or the length of time subjects spent in treatment. Moreover, this study lacked a control group.

A major problem with Rosenthal et al.'s (1984,1985b) studies is that sleep deprivation may account for the observed effects. Since subjects received light exposure three hours before dawn, they may have been partially deprived of sleep. As noted earlier, sleep deprivation in the second half of the night has an antidepressant effect in some patients (von Zerssen, 1983). Although no significant antidepressant responses were noted in patients under dim light, the results may have been biased towards the bright light condition. Rosenthal et al. (1984) report that they found "... a significantly higher number of low activity scores in patients under dim light conditions than in bright light which strongly suggests that more sleep occurred under these conditions." (p.78). This makes it difficult to separate out the possible effects of sleep deprivation from phototherapy. Although sleep was not monitored in Rosenthal et al.'s (1985b) outpatient study it is likely that this study suffered from similar problems. They report that close observation during the inpatient study ensured that no subject slept during either light exposure.

James, Wehr, Sack, Parry, and Rosenthal (1985) lengthened the winter photoperiod by exposing nine female seasonal depressives to bright (2500 lux) or dim (300 lux) light. Subjects self-administered light in their own homes for five hours in the evening either between 1800h and 2300h or 1900h and 2400h. The same four week protocol was used as in the previous studies. The results showed that Hamilton Rating Scale scores were significantly reduced after bright but not after dim light. When compared with Rosenthal et al.'s (1984,1985b) results where subjects were exposed to both morning and evening light, no significant differences were found. The authors concluded that bright light in the evening is equally as effective as a combined morning and evening schedule in producing the antidepressant response.

This study, however, lacks rigorous control. Subjects were permitted to choose their own light schedules, allowing for variability in the times of exposure. Also, it is not clear whether subjects were observed during exposures nor do the authors report whether subjects spent time away from the lights or slept during exposures. Unfortunately, these problems are not unique to this study and will be more fully discussed later in this chapter.

A partial replication of Rosenthal et al.'s (1984,1985b) studies was conducted by Wirz-Justice, Bucheli, Graw, Kielholz, Fisch, and Woggon (1986). They treated seasonal depressives, identified in a Swiss-German population, with bright (2500 lux) and dim (250 lux) light using the counterbalanced cross-over procedure employed by previous studies. Four subjects completed the cross-over. They were exposed to light from 0600h to 0800h and 1800h to 2000h daily. In contrast to previous findings, improvement (defined as a decrease of five or more points on the Hamilton Rating Scale) occurred under both conditions. No significant differences were noted for bright or dim light before or after treatment. Differences were found in response to withdrawal from treatment. One week later depression scores had returned to pre-treatment values for the dim but not the bright light condition.

The authors suggest that the strict application of SAD criteria for inclusion in this study resulted in the selection of a subgroup of bipolar patients who are biologically sensitive to light. This is based on Lewy, Nurnberger, Wehr, Pack, Becker, Powell and Newsome's (1985) finding that some bipolar patients exhibit melatonin suppression at dim intensities (500 lux) whereas others do not.

It could be argued that the lack of a difference between bright and dim conditions found in Wirz-Justice et al.'s (1986) study is the result of poorly controlled experimental conditions. The authors report that some subjects sat closer to the dim lights than required, and thereby increased the intensity of exposures. Another possible explanation for these results is that the subjects were responding to placebo effects. The expectation of improvement may have resulted in a reduction of depressive symptoms under dim light.

Studies of the External Coincidence Model

Kripke, Risch, and Janowsky (1983a) awakened 12 Major Depressives at 0500h and exposed them to one hour of bright light (1000-2000 lux). On another night subjects were awakened at the same time and exposed to a dim red light control (25 lux). Treatments were counterbalanced across subjects, randomly assigned to conditions. Subjects were rated on the Hamilton Rating Scale and the Beck Depression Inventory before and after

light treatment. Bright white light significantly lowered both Hamilton and Beck ratings compared to baseline. Depression ratings after bright white light were significantly lower than after dim red light. The dim red light treatment produced no significant improvement in the Beck scores, although a 'marginally significant' improvement was noted on the Hamilton ratings.

The lack of a control group who were not receiving light exposure during early morning makes sleep deprivation a major rival explanation for these effects. Hence a second study was conducted which attempted to control for this.

Following one day of baseline, Kripke, Risch and Janowsky (1983b) subjected 12 volunteer Major Depressives to three one hour awakenings on three subsequent nights. The three conditions were: (a) exposure to bright light (1000-2000 lux) one to two hours before the usual time of arising; (b) exposure to dim red light (25 lux) one to two hours before usual time of arising; (c) control awakening two to three hours after bedtime with exposure to dim red light. Treatments were counterbalanced across subjects and followed by ratings on the Hamilton. Subjects were monitored to ensure that they remained awake. Results indicated that Hamilton ratings were significantly lower after bright light exposure than after dim red light. Neither the control awakening or dim light condition had any antidepressant effect.

A number of problems are apparent in these studies with respect to the heterogeneity of samples and the appropriateness of subjects for phototherapy. In Kripke et al.'s (1983a) study nine patients were diagnosed as having Primary Depressive Disorder (Research Diagnostic Criteria) and two were given diagnoses of depression secondary to alcoholism. Three bipolar depressives were included as well as one patient, displaying depressed mood at the time of the experiment, who later received a diagnosis of hypochondriasis. Patients were not screened for the existence of circadian rhythm disturbances. Furthermore, it is not clear whether any endogenous or seasonal depressives were included. The majority of subjects, however, appear to be unsuitable for phototherapy. A placebo response appears likely especially since results from the first study indicated that the dim light control had an antidepressant effect.

Kripke et al. (1983b) provide no information as to subjects' diagnoses or their suitability for light treatment. In addition, it is not clear whether some or all of these subjects had participated in the previous study. If this was the case subjects may have been more likely to respond to the bright light condition, based on their conceptions from previous treatments. This is highly probable in view of the fact that all subjects were volunteers and highly motivated to participate.

Studies of the Phase Response Curve Model

Lewy, Sack, Miller, and Hoban (1987) investigated the predictions proposed by the phase response curve model with respect to phototherapy in seasonal depressives. Eight seasonal depressives and seven normal controls were confined to indoors between 1700h and 1800h and shielded from bright light. Experimentation was carried out under laboratory conditions and subjects were permitted to sleep only between 2200h and 0600h. During the first week baseline measures (Hamilton Rating Scale scores and melatonin assays) were taken. In the second week subjects were randomly assigned and exposed to either morning bright light (2500 lux) from 0600h to 0800h or evening bright light from 2000h to 2200h. In the third week these exposures were reversed. In the fourth week subjects were given both morning and evening light exposures.

Following a week of morning light, depression ratings were significantly lower compared to baseline and not significantly different from those of healthy controls. The melatonin rhythm, which was found to be significantly phase-delayed at baseline, advanced to a phase position similar to that of normal controls. In contrast, ratings of depression following evening light were not significantly different from baseline and were significantly greater than after morning light. Evening light delayed melatonin onset in both patients and controls. The morning and evening light combination shifted melatonin onset to an intermediate phase position. This shift was accompanied by an antidepressant response. The authors suggested that morning and evening light together counteract each other, thereby reducing the circadian shifts induced by one another.

Yerevanian, Anderson, Grota, and Bray (1986) compared the responses of nine seasonal depressives with eight endogenous depressives to bright light. Subjects who reported early morning wakening began on evening phototherapy (from 2000h to 2200h) while subjects with morning hypersomnia began on morning phototherapy (from 0530h to 0730h). The remaining three subjects were randomly assigned to either morning or evening treatment. Light exposure (>2000 lux) was administered for seven consecutive days. Subjects were assessed on the Hamilton Rating Scale, the Beck Depression Inventory, and the Global Assessment Scale following the fourth and seventh exposures. Eight subjects who remained depressed following this treatment were crossed over to the other treatment time for one week. Outpatients, primarily seasonal depressives, self-administered their light exposures. Inpatients, mostly endogenous depressives, received phototherapy under hospital supervision.

The seasonal depressives were found to significantly improve following bright light whereas endogenous depressives did not. All seasonal depressives met the criteria for recovery: Final Hamilton Score less than 10; final Hamilton score less than 50% of the pre-treatment score; failure to meet DSM-III criteria for Major Depressive Disorder. None of the endogenous depressives fulfilled these criteria.

These results are subject to a number of interpretive difficulties. Differences between the two groups were apparent both before and after phototherapy. The seasonal group showed a significantly higher level of overall functioning prior to treatment. Only three seasonal subjects were receiving medication whereas all non-seasonal subjects were on antidepressants. The non-seasonal depressives were more severely depressed. Baseline scores showed that they were, on average, six points higher on the Hamilton than the seasonal depressives and five points higher on the Beck. Since the criteria for recovery were largely related to Hamilton change scores it was easier for the seasonal depressives to meet these requirements.

These problems are compounded because the administration of phototherapy largely differed between the two groups. Seasonal depressives, who were mostly outpatients, were essentially uncontrolled in the use of light being responsible for their own light administration. Endogenous

depressives (all inpatients) received phototherapy under controlled conditions in a hospital environment. The lack of control over environmental conditions during light administrations for seasonal depressives is a major confounding variable in this experiment.

Another major factor which could account for differential responses between the two groups is the way in which subjects were selected. Seasonal depressives were generally recruited via a newspaper article whereas endogenous depressives were selected from the psychiatric population. Seasonal volunteers therefore may have been more motivated to respond to treatment.

Studies Testing Multiple Models

Hellekson, Kline, and Rosenthal (1986) attempted to test the photoperiodic and phase response curve models by exposing six seasonal depressives to three different one week bright light (2500 lux) schedules. Using a single blind cross-over design, subjects were administered the following schedules: (a) One hour of light treatment followed by one hour fourteen hours later; (b) Two hours of light treatment in the evening; (c) Two hours of light treatment upon arising in the morning. Order of treatments was counterbalanced across subjects and each condition was separated from the other by one week of no treatment. Hamilton ratings of depression were gathered at baseline and at the end of each week. Results indicated a significant difference between baseline and treatment conditions for all treatments. No significant differences were noted between treatment schedules. Significant relapse occurred when light was withdrawn.

This experiment has some major shortcomings. Subjects were not specifically instructed to avoid bright light in the morning when receiving evening light only. Similarly, when on the morning only schedule subjects should have avoided bright light in the evening. It is possible that subjects may have been receiving light in a similar way to that provided by protocol (a). This would account for the lack of a significant difference between treatment schedules. Assuming patients were responsible for their own administration of light exposures, the lack of control over environmental conditions would increase the probability of this occurring.

Wehr, Jacobsen, Sack, Arendt, Tamarkin, and Rosenthal (1986) sought to determine whether the duration (photon-counting hypothesis) or the timing (photoperiodic model) of light is necessary for the antidepressant response. This was done by using long and short skeleton photoperiods. The Long Skeleton Photoperiod (LSP) involved lengthening the light period by administering light before dawn (0730h to 01030h) and after dusk (2000h to 2300h). The Short Skeleton Photoperiod (SSP) required that light be given late in the morning (from 0900h to 1200h) and early in the afternoon (from 1400h to 1700h).

Seven seasonal depressives (four female, three male) were subjected to bright light (2500 lux) according to the schedules set out by the LSP and SSP. The two treatments (each of five days duration) were administered in a balanced randomized cross-over design with at least nine days between treatment periods to allow for relapse. Results showed that both treatment schedules were effective in reducing depressive symptoms and that there were no significant differences between them. The authors concluded that the timing of light was not important in eliciting the antidepressant response.

On completion of this experiment the authors investigated the melatonin-suppression hypothesis by looking at the effects of the SSP on melatonin secretion. Three subjects who had initially responded to the SSP were again exposed to the SSP after relapse into depression. Blood samples were taken every hour for 48 hours. Room lighting and experimental conditions were the same as in the previous study. Subjects rated their mood every two hours while awake on a 24-point visual scale. Mood showed marked improvement after one day of treatment with the SSP but plasma melatonin levels did not decrease.

Wirz-Justice, Schmid, Graw, Krauchi, Kielholz, Poldinger, Fisch and Buddeberg (1987) also investigated the importance of the duration of phototherapy. They exposed 15 seasonal depressives to half an hour or two hours of bright light beginning at 0600h. Treatments were self-administered in subjects' own homes using a four week counterbalanced cross-over design. Subjects received one duration of light for one week followed by a weeks' withdrawal and one week with the other duration. Measures of depression

were taken at the end of each week and one week following the second treatment. Nine other subjects were treated using one hour of bright light for one week. Two hours of bright light was found to significantly improve depressive symptoms independent of order whereas half an hour did not. Seven out of the nine subjects who were on the one hour light schedule also reduced their depression ratings.

While the duration of light appears to be important in producing an antidepressant response, one cannot conclude that duration alone was responsible for the observed effect. Light was administered during the morning hours only, the phase of the light-dark cycle in which bright light exposure is expected to produce the maximum antidepressant effect in seasonal depressives (Lewy et al., 1983). It may be that the timing of light is an additional factor necessary for an antidepressant response.

Other Studies

Several studies have concentrated upon the biological effects of light rather than testing formal models. Dietzel, Saletu, Lesch, Sieghart, and Schjerve (1986) investigated the effects of bright light in a group of 10 female endogenous depressives compared to 10 normal subjects. Both groups were exposed to a one day baseline condition, then one days' exposure to bright light (2800 lux) between 0600h to 0900h and 1700h to 2100h, at times similar to studies testing photoperiodic models. This was followed by a one day recovery period. At baseline depressives were found to have an increased sleep latency, decreased total sleep time, a shortened REM latency, and significantly increased REM length compared to normals. Plasma cortisol peaks were noted to occur significantly earlier and the amplitude of the rhythm was significantly higher in the depressives than in the controls. Temperature minima also occurred earlier in the depressives. Ratings of depressed mood were significantly higher in the patients than in the controls.

After the administration of bright light sleep onset was shortened, REM latency increased, and the average length of REM sleep was significantly attenuated. Subjective ratings of well-being via a visual analogue scale significantly improved after bright light. There were no significant

differences between depressives' and controls' ratings of well-being following phototherapy. The advanced peaks of plasma cortisol disappeared although temperature rhythms were not greatly affected.

Questions can be raised as to whether one day of light exposure is sufficient to produce an antidepressant effect. Previous studies have indicated that this effect occurs within two to four days of treatment. Also, one would also expect the antidepressant response to be accompanied by a shift in biological rhythms. However, only REM sleep showed a significant shift suggesting that the magnitude of responses regarding well-being may have been influenced by subjects' expectations. The lack of observer measures of depression makes this a viable possibility.

Wehr, Skwerer, Jacobsen, Sack, and Rosenthal (1987) attempted to determine whether the eyes are important mediators for the effects of light. They administered 2500 lux of bright light to 10 (nine female, one male) seasonal depressives. Subjects were exposed to two treatments using a counterbalanced cross-over design similar to that used in other studies (for example, Rosenthal et al., 1984). One treatment condition involved exposing the subjects' face, neck and arms, but not eyes to bright light while the other involved light exposure to the eyes only. Treatments were given in the evening (1830h to 2230h) for one week. This was separated by a week of no light and then cross-over to the other condition. Hamilton ratings before and after treatments showed that exposure to the eyes significantly reduced scores whereas exposure to the skin did not.

However, three subjects had prior experience, and probably preconceived ideas, of phototherapy. Subjects correctly predicted the outcome in seven out of eight cases. Clearly, further research is needed before such results can be regarded as conclusive.

Implications of Results for Theories of Phototherapy

Following a review of the research findings in the area of phototherapy it seems appropriate to consider the evidence for and against the predictions proposed by the various theoretical positions.

To recapitulate, the photoperiodic model predicts that extending the hours of daylight to the equivalent of a spring/summer photoperiod will bring about remission in seasonal depressives. This prediction is supported by a number of studies in which bright light was administered at both extremes of the photoperiod (Dietzel et al., 1986; Hellekson et al., 1986; Lewy et al., 1982; Rosenthal et al., 1984,1985b; Wehr et al., 1986; Wirz-Justice et al., 1986). Additional support is provided by studies which lengthened the photoperiod by administering bright light either at either dawn or dusk (Hellekson et al., 1986; James et al., 1985; Kripke et al., 1983a, 1983b; Lewy et al., 1987; Wirz-Justice et al., 1987; Yerevanian et al., 1986; Wehr et al., 1987). Wehr et al.'s (1986) finding that a short skeleton photoperiod lowers depression ratings fails to support the photoperiodic model.

The external coincidence model, which predicts that bright light given at the individual's usual time of awakening will reduce symptomatology in endogenous depressives, also receives some support (Kripke et al., 1983a, 1983b).

The phase response curve model generates a number of related predictions, some of which are supported by the current research. This model suggests that administering bright light during the morning hours will produce the optimum antidepressant effect in seasonal depressives. The findings of Lewy et al. (1987), Wirz-Justice et al. (1987), and Yerevanian et al. (1986) support this prediction. The phase response curve model also predicts that light given during normal daylight hours will not produce an antidepressant effect. This prediction is contrary to the findings of Wehr et al. (1986). A further prediction arising from this model, that bright light given in the evening will produce the optimum antidepressant response in endogenous depressives, has yet to be tested.

Although not explicitly stated by the phase response curve, this model appears to suggest that a combination of morning and evening light will produce some reduction in depressive symptoms. However, a lesser antidepressant response is expected on the basis of this model since the light given at dusk would, to some extent, counteract the beneficial effect of light administered at dawn. Hence the phase response curve model is consistent with the findings of Dietzel et al. (1986), Hellekson et al. (1986),

Lewy et al. (1987), Rosenthal et al. (1984, 1985b), and Wirz-Justice et al. (1986).

The photon-counting hypothesis, which predicts that the duration of light is critical for the antidepressant response, is supported by Hellekson et al. (1986), Wehr et al. (1986) and Wirz-Justice et al. (1987). Although this hypothesis does not specify the duration of exposure required to produce an antidepressant response, all of the studies presented here involved lengthy (between two to seven hours) daily exposures to light. Hence these studies can, to some extent, be viewed as support for this hypothesis.

Finally, the melatonin-suppression hypothesis predicts that bright light of sufficient intensity to reduce melatonin will reduce depression. Most studies which have included both bright and dim conditions support bright but not dim light as having an antidepressant effect (James et al., 1985; Kripke et al., 1983b; Rosenthal et al., 1984,1985b). Although intensity appears to be an important factor, the melatonin-suppression hypothesis is not supported by Wehr et al. (1986) who found that depression ratings but not melatonin levels were reduced following exposure to bright light.

Methodological Problems

Many of the studies reviewed here, however, can only be regarded as tentative support for these theories. The previous discussion highlights some of the major interpretive difficulties relating to studies of phototherapy in depressives. Some of the methodological problems associated with these studies bear further discussion. Studies of phototherapy can be criticized in terms of selection, small sample size, inadequate control over experimental conditions, experimental design, reliability, and placebo effects.

Selection

Ten studies recruited seasonal depressives by means of newspaper advertisements (Hellekson et al., 1986; James et al., 1985; Lewy et al., 1987; Rosenthal et al., 1984,1985b; Wehr et al., 1986,1987; Wirz-Justice et al., 1986,1987; Yerevanian et al., 1986). One of these advertisements suggested that " ... changes in the light might be responsible for ... mood changes and

invited persons with seasonal mood changes to contact (them)." (Rosenthal et al., 1984, p.72). Although individuals were screened and only those who met the criteria for SAD included, the samples may have been biased in a number of respects.

First, all subjects were self-referred. Second, all subjects were sufficiently motivated to follow-up on the advertisements. This suggests that subjects had certain (favourable?) expectations about the treatment which may have biased their responses.

The method of selection also raises questions regarding external validity. Recruiting subjects through advertisement immediately excludes that portion of the SAD population who are unaware of the article or who are not motivated to follow it up.

Some studies have also stipulated additional inclusion criteria thereby making samples more selective. Some require a score of at least 10 points (Rosenthal et al., 1985b), 13 points (Helleksen et al., 1986), 14 points (James et al., 1985) or 15 points (Wirz-Justice et al., 1986,1987) on the Hamilton Rating scale. Thus all individuals must be at least moderately depressed. This excludes individuals at the lower end of the range. Moreover, it is not known whether severely depressed patients are adequately represented. Some studies also appear to have applied the criteria for SAD more stringently than others (Wirz-Justice et al., 1986) thus increasing selection bias.

Threats to internal validity are apparent in some studies which have included subjects on medication. Antidepressants may work through similar mechanisms as phototherapy making it impossible to separate out these effects. Many studies have reported the inclusion of subjects on medication. James et al. (1985) and Rosenthal et al. (1984,1985b) note that one subject was currently receiving medication. Kripke et al. (1983a) report concurrent use of antidepressants in three subjects while three seasonal and all (eight) non-seasonal subjects in Yerevanian et al.'s (1986) study were on medication. It is not clear from the reports of Hellekson et al. (1986), Kripke et al. (1983b), Wehr et al. (1986,1987), and Wirz-Justice et al. (1987) whether subjects were medication-free.

Sample Size

Studies of phototherapy have usually involved small numbers of subjects. Sample size ranges from a single subject (Lewy et al., 1982) to a sample of fifteen SAD patients (Wirz-Justice et al., 1987). Most studies have included between seven to twelve subjects. In view of these small numbers, questions regarding external validity must be raised. It is difficult to assess external validity in studies which supply limited demographic information. Kripke et al. (1983a,1983b), Lewy et al. (1987) and Wirz-Justice et al. (1987) supply no information as to the number of males and female subjects. Additionally, some studies do not report subjects' ages (Kripke et al., 1983a,1983b; Lewy et al., 1987; Wehr et al., 1986,1987; Wirz-Justice et al., 1987). Some studies have used only females (Dietzel et al., 1986; Helleksen et al., 1986; James et al., 1985; Yerevanian et al., 1986). Therefore there may be a selection bias against males.

Inadequate Control Over Experimental Conditions

Six studies were conducted in which seasonal subjects received light exposures in their own homes (James et al., 1985; Rosenthal et al., 1984,1985b; Wirz-Justice et al., 1986,1987; Yerevanian et al., 1986). Light was self-administered and subjects were not observed during light exposures. These conditions pose a number of serious experimental weaknesses.

A major problem is that due to the lack of observations, there was no control over the amount of time spent under the lights. Subjects were not forced to adhere to the treatment regimens and could effectively spend as much or as little time under the lights as they wished. Subjects apparently did not always spent the required amount of time under the lights. Rosenthal et al. (1985b) report that in their outpatient study subjects spent an average of 4.5 hours of the time they should have been receiving dim light away from treatment. Seven and a half hours per patient was spent away from the bright light condition. Only three of these outpatient studies (James et al., 1985; Rosenthal et al., 1984,1985b) report that subjects kept a written record of time away from light treatment. These reports, though, depend on the accuracy, and to some extent honesty, of the subjects themselves who may already feel pressured to live up to the expectations of the treatment. The

lack of observation ensuring equal amounts of time spent under each lighting condition is a serious weakness of these studies.

A second problem posed by lack of observation during treatment is that it is impossible to objectively gauge sleep during exposures, particularly early morning treatments. In some cases there is evidence to suggest that subjects did sleep, or at least closed their eyes, during exposure. Rosenthal et al. (1984) report that wrist activity recordings during morning treatments showed a significantly larger number of low value counts. They suggest that sleep occurred under dim light. In Rosenthal et al.'s (1985b) outpatient study sleep was monitored by morning telephone calls and self-reports of alertness at 15 minute intervals. Even under these conditions a "small" amount of sleep was noted (Mean=3.3 and 5.2 minutes per patient per day under bright and dim light respectively). These calculations, however, largely depend upon the reliability of patients self-reports.

Other studies, with the exception of Yerevanian et al. (1986), have relied heavily upon self-report to determine the amount of sleep obtained. None of these studies, however, gathered reports of the frequency with which subjects closed their eyes during each treatment. This is important since the effects of light therapy are assumed to be mediated by the eyes. One might expect subjects would be apt to close their eyes more frequently under the dim light condition thus creating a possible bias towards bright light.

A further problem posed by conducting experimentation in patients homes is that the intensity of light cannot be controlled. Light intensity depends upon the size of the room and will vary in different parts of the room. In these studies light intensity is measured at eye level from a fixed sitting position. As subjects move closer to or away from the light, intensity increases or decreases accordingly. Since subjects were not monitored, they were free to move about the room and would have been exposed to varying light intensities. Wirz-Justice et al. (1986) report that some subjects in their study moved "...nearer the yellow lights ("because they were dimmer") " (p.202). Thus the actual intensities to which subjects were exposed under each condition cannot be precisely quantified. Kripke et al.'s (1983a,1983b) studies are subject to similar criticisms since subjects were not required to remain in a fixed position during light exposures.

Dim Light Control

Studies which have included a dim light condition have, in some cases, coloured the light to distract subjects from believing that bright white light is the active treatment. Some studies have used dim red (Kripke et al., 1983a,1983b) while others have used dim yellow light (Rosenthal et al., 1984; Wirz-Justice et al., 1986). Yellow light appears to be a less effective disguise. Four out of six subjects in Rosenthal et al.'s (1984) study predicted that bright white light would be more helpful. One patient thought the lights would be equally effective. Kripke et al. (1983a) note that "half" the staff responsible for observing subjects thought that the red light was the active treatment.

In their second study Kripke et al. (1983b) report that "many patients and staff thought that the dim red light was the active treatment" (p. 528) but we are not told as to how this information was obtained or the relative proportion of subjects who held this belief. Wirz-Justice et al. (1986) did not study subjects expectations regarding their yellow light control. It is uncertain whether a coloured control light has the capacity to act as a viable placebo for bright white light in these treatments.

Certainly dim white light appears to be an implausible control. Rosenthal et al. (1985b) used dim white light controls (5 lux for inpatients; 300 lux for outpatients) as did James et al. (1985). The extremely dim light control (5 lux) used in Rosenthal et al.'s (1985b) study further reduced its capacity to act as a viable control. In other words, the difference between the two lighting conditions was so great that subjects could not fail to perceive differences between the treatments. Similar to research findings which show that a large placebo pill is more effective than a small one (Gruber, 1956; Rickels, Hesbacher, Weise, Gray, and Feldman, 1970), the more intense light may have a more substantial placebo effect than the dim light. Thus the results may be biased in favour of bright white light.

A number of studies have not used a dim light control condition (Dietzel et al., 1986; Hellekson et al., 1986; Lewy et al., 1982,1987; Wehr et al., 1986; Wirz-Justice et al., 1987; Yerevanian et al., 1986). While one may argue that these studies by using bright light only, more effectively disguised the

regimen expected to be most effective, subjects responded to light treatments in all cases. Thus a placebo or demand characteristics explanation cannot be excluded.

Reliability

Studies have generally used validated rating scales and some have used self-report measures (the Beck Depression Inventory) in addition to observer ratings (Kripke et al., 1983a,1983b; Rosenthal et al., 1984; Yerevanian et al., 1986). Dietzel et al.'s (1984) study can be criticized for using only a self-report scale. Self-report measures alone may be of limited use in an experiment of this kind as subjects may respond in a way they perceive to be socially desirable or according to demand characteristics. However, all other studies have involved observer measures of depression and, with the exception of Lewy et al. (1982), have used the Hamilton Rating Scale.

In some cases no information is given as to whether observers conducting the ratings were blind to the treatment condition. Neither is there any indication of inter-rater reliability (Kripke et al., 1983b; Lewy et al., 1982,1987; Rosenthal et al., 1985b). Wirz-Justice et al. (1987) and Yerevanian et al. (1986) both used a single rater to determine patients responses on the Hamilton. In the latter study the rater was not blind to the treatment condition. This is not clear in the first study but it is likely that the measure of response was subjective rather than objective. Other studies have employed two raters both blind to the treatment conditions but none report the degree of inter-rater reliability (James et al., 1985; Kripke et al., 1983a; Rosenthal et al., 1984; Wehr et al., 1986,1987). Only one study (Hellekson et al., 1986) used two raters and reported a high degree of agreement between them (r=0.92).

An additional problem arises with respect to the measures used in most studies of seasonal depressives. The Hamilton Rating scale does not fully reflect the symptoms of depression in SAD. Symptoms such as hypersomnia, overeating, weight gain, and carbohydrate craving are not represented at all on this scale. The Beck Depression Inventory can be criticized in the same way. Out of the 10 studies that have involved SAD patients only one (Wehr et al., 1986) has used additional measures to assess depressive symptoms not

addressed by these other scales. Unfortunately, these measures were invalidated.

Experimental Design

A major weakness of many of the studies reviewed here is the choice of experimental design. Seven studies have employed a 4 week counter-balanced crossover experimental protocol (James et al., 1985; Rosenthal et al., 1984,1985b; Wehr et al., 1986,1987; Wirz-Justice et al., 1986,1987). Although subjects serve as their own controls, this design allows for the possibility that subjects may improve over the mere passage of time. This spontaneous remission does not necessarily have anything to do with the treatment conditions. Time series designs such as this may be threatened by external events such as the change of season. If these studies began, say a month before the end of winter, when spring is approaching, the likelihood of remission is increased. This occurrence appears to have been a problem in Helleksen et al.'s (1986) study. They used a similar design but added another treatment and corresponding withdrawal conditions. Patients in their study were subjected to a seven week protocol and the latter part of the study coincided with the beginning of spring.

Problems of spontaneous remission may have also been operating in Lewy et al.'s (1987) 4 week counter-balanced cross-over protocol. This design is subject to additional criticism due to the omission of a washout period between the treatment conditions. This allows for possible carryover of the effects of one treatment administration to the next.

Other studies have minimized the occurrence of spontaneous remission by designing experiments conducted over very short time periods. Lewy et al. (1982) used a simple pretest-posttest design with only nine days between before and after treatment measures. However, the design is weakened considerably due to the lack of a control group. Improving upon this, Dietzel et al. (1986) used a similar design but both endogenous depressives and healthy controls were subjected to the same experimental procedures. Subjects were exposed to light treatment for a single day. It is as yet unclear whether a single day's exposure to bright light is sufficient to produce the dramatic changes in mood noted by Dietzel et al. (1986). Other

studies which exposed subjects to light treatment for a single day are also open to question (Kripke et al., 1983a,1983b).

Yerevanian et al.'s (1986) study is unique in that two groups of depressives - endogenous and seasonal are compared. Subjects were exposed to bright light for two hours either morning or evening for one week. However, the majority of subjects were not randomly assigned to these treatments and only those who were still depressed following the first treatment were crossed over to the other treatment.

Placebo Effects

Placebo explanations are probably the greatest threat to the internal validity of these light studies. Determination of subject expectations are of paramount importance so that these effects can be separated from treatment effects. Dim light may not be an effective placebo control if subjects expect dim light to be inactive or less active than bright light.

As previously noted, subject expectations appears to be a plausible reason for the observed results in many studies. Four out of six patients in Rosenthal et al.'s (1984) study predicted that bright light would be more helpful than dim yellow light. In Wehr et al.'s (1987) study subjects expectations correctly predicted the outcome in seven out of eight cases. Other studies, with one exception, did not investigate patients expectations with respect to treatments. On a more positive side, Wirz-Justice et al. (1987) note that their group did not differ in their predictions of which treatment (half an hour, one hour, or two hours) would be more effective. However, subjects and observer ratings of treatments following the study judged half an hour as having no effect in contrast to one or two hours of light.

Other factors operating in these experiments may have increased the possibility that subjects expectations may have determined their responses. A number of authors (for example, James et al., 1985) have noted that there has been a great deal of publicity about phototherapy in recent years. These reports appear to suggest that potential subjects may be aware of the expected efficacy of bright light over dim light. This increases the likelihood

that subjects will have preconceived ideas about therapy before entering study. Yerevanian et al. (1986) report that "... one of our seasonal patients asked specifically for 2500 lux!" (p. 362). It is not clear how many studies were affected by such publicity. Knowledge of treatments may have been more problematic in studies conducted in patients' homes. Subjects in the dim light condition may have sat closer to the lights to increase intensity or may have used auxiliary lighting to simulate the bright light condition.

Although some studies have attempted to use more controlled conditions by observing subjects in the laboratory, placebo effects may still be operating. This is likely if subjects were treated at the same time as in Kripke et al.'s (1983a,1983b) studies. This also raises the possibility that depressed subjects improve simply by being in a room with others who are perceived to have similar problems. It is not clear from the reports of Dietzel et al. (1986), Hellekson et al. (1986), Lewy et al. (1987), Wehr et al. (1986,1987), Yerevanian et al. (1986, inpatient study), whether subjects were treated together or individually.

None of the mentioned studies controlled for subjects activities during light exposure. Subjects were allowed to read, listen to music, watch television, or socialize under the lights. The socialization aspect and the psychological impact of receiving 'special' treatment may influence mood. A relapse into depression once the treatment is withdrawn, as is usually found to be the case, would be expected.

Placebo effects are most likely to operate in studies whose subjects have had previous experience with phototherapy as it is unlikely that these subjects will be blind to the treatments. Wehr et al. (1987) report that three of their ten subjects had prior experience with light treatments. Kripke et al. (1983a) note that seven out of twelve subjects in their study had previous exposure to bright light. Subjects in Rosenthal et al.'s (1985b) study of evening light had similar experience. It is not clear whether subjects in other studies (Kripke et al., 1983b; Wirz-Justice et al., 1987) had received light treatment before study. Only Wehr et al. (1986) note that all subjects had no previous exposure to this type of treatment.

In summary small sample size, use of subjects on medication, lack of control over experimental conditions, poor experimental design, use of single or non-blind raters on objective measures of depression, and placebo effects are weaknesses of many of the studies conducted in the area of phototherapy. Future studies must exert tighter control over these factors before definite conclusions regarding the antidepressant properties of phototherapy can be drawn.

Best Controlled Studies

From the previous discussion it is evident that most studies reviewed here are limited in their usefulness as support for the various theoretical positions. Many of the studies presented demonstrate major problems, both in the interpretation of results and research methodology. Although these studies have been criticized for their shortcomings, it is important to bear in mind that no study can control for all factors. However, many of the problems evident in the literature could have been avoided.

Of the 14 studies reviewed two studies emerge from the literature as being the most valid (Lewy et al., 1987; Wehr et al., 1986). Although both studies, by design, are subject to problems of placebo effects, spontaneous remission and small subject numbers, they have some advantages over many studies in this area. Both include extensive measurements of melatonin, allowing for observation of the effects of light on this rhythm. Furthermore, experimentation was conducted under conditions which control for light intensity, sleep, and duration of exposures. It therefore seems appropriate to consider the findings from these studies in terms of support for the theoretical positions which they are designed to test.

To recapitulate, Wehr et al. (1986) found no significant difference in the antidepressant response to bright light administered according to a long skeleton photoperiod (0730h to 1030h and 2000h to 2300h) and a short skeleton photoperiod (0900h to 1200h and 1400h to 1700h). This supports the photon-counting hypothesis which suggests that the duration rather than the timing of light is important for the antidepressant response. The antidepressant response associated with the long skeleton photoperiod is also consistent with the photoperiodic model. However, the photoperiodic model

cannot account for the effectiveness of the short skeleton photoperiod. In addition, the finding that the short skeleton photoperiod improved mood but did not decrease plasma melatonin, fails to support the melatonin-suppression hypothesis.

The findings of Wehr et al.'s (1986) study are also consistent with the phase response curve model. Since the morning light exposures of the two photoperiods overlapped, the phase response curve can explain this result. If the phase-shift model is correct, one would expect either photoperiod to produce an antidepressant effect on the basis that both lighting schedules were capable of advancing circadian phase position in seasonal depression. The long skeleton photoperiod might not have been more effective because its later evening light (2000h to 2300h compared to 1400h to 1700h for the short photoperiod) could have been counteracting the greater phase advance shift from its earlier morning light.

Lewy et al.'s (1987) findings are also in support of a phase response curve model. A week of morning bright light significantly lowered depression ratings in seasonal depressives whereas a week of evening light did not. Morning light advanced melatonin onset whereas evening light delayed it. A combination of morning and evening light produced an intermediate antidepressant response and correspondingly shifted melatonin onset to an intermediate phase position.

Clearly, the results of these studies must be regarded tentatively. However, they do appear to suggest that both the phase response curve model and photon-counting hypothesis are worthy of further investigation.

Summary

Research findings suggest that bright light is effective in ameliorating depressive symptoms in individuals with circadian rhythm disturbances. Although the research generally supports the predictions made by the photoperiodic, external coincidence, and phase response curve models, interpretive difficulties and serious methodological problems apparent in many studies raises questions as to the validity of these findings.

Many experiments have been conducted under conditions which lacked control over the duration, light intensity, and the amount of sleep during light exposures. In addition, studies have generally included small numbers of subjects and have, in some cases, included subjects receiving concurrent medication. Observer ratings of depression have often involved single raters and/or non-blind raters. Studies have generally failed to report the degree of reliability between raters.

A major problem with many studies lies in the experimental design. Most studies have employed counterbalanced cross-over time series designs ranging from four to seven weeks duration. This design increases the likelihood of spontaneous remissions, particularly in cases where experiments of seasonal depressives have extended into spring. Only one study (Yerevanian et al., 1986) compared groups of seasonal and endogenous depressives. However, these groups were non-equivalent with respect to the severity of depression, medication, and the conditions under which phototherapy was administered.

Placebo effects could certainly explain the antidepressant responses of depressives in these studies. No study has adequately controlled for this factor. The methods of selection used to obtain seasonal subjects, publicity through the media, use of subjects with previous experience of phototherapy, and lack of control over subject interactions during exposures are common to many studies. All these factors influence subjects expectations of treatment. Two out of three studies found that subjects expectations correctly predicted the outcomes in the majority of cases when this factor was explicitly evaluated.

Major weaknesses in many studies limits their usefulness as evidence for the theoretical positions proposed to explain the antidepressant action of light. However, two studies, which appear to be the most methodologically sound, provide support for the photon-counting hypothesis (Wehr et al., 1986), the phase response curve model (Lewy et al., 1987; Wehr et al., 1986), and partial support for the photoperiodic model (Wehr et al., 1986). The melatonin-suppression hypothesis gains little support.

CHAPTER SEVEN: CONCLUSIONS AND FUTURE CONSIDERATIONS

Discussion up to this point has focussed on a number of issues with respect to the therapeutic potential of phototherapy. These have included consideration of the characteristics of depressed individuals who may be most likely to respond to phototherapy, the various theoretical positions which explain the mechanisms of the antidepressant action of light, and the research to support phototherapy as being an effective treatment for some types of depression. An analysis of studies in this area elucidates the paucity of well-controlled research to support the efficacy of phototherapy. Despite this fact, several lines of evidence can be viewed as support for the ability of light to reduce depressive symptoms:

1. Research shows that bright light has the capacity to entrain the human circadian system. Bright light has been found to shift the circadian rhythms of both endogenous and seasonal depressives to a more normal phase position and to produce a corresponding decrease in ratings of depression (Dietzel et al., 1986; Lewy et al., 1987). These findings are also consistent with the view that light has a biologically active effect and that correction of the circadian systems of some depressives has a corresponding antidepressant effect.

2. Reduction in depressive symptomatology following exposure to bright light is a consistent finding in studies of phototherapy. Although many studies have serious limitations, the most carefully controlled studies are consistent with the view that bright light has an antidepressant effect (Lewy et al., 1987; Wehr et al., 1986).

3. Studies generally show that improvement in symptomatology is seen within two to four days of beginning bright light and relapse occurs within a similar time period. According to Wirz-Justice et al. (1986) "...relapse after withdrawal is considered a criterion for an active agent.." (p. 201).

4. The use of bright light has been shown to lead to repeated improvement in the same individual. Some experimenters have allowed

seasonal patients to use bright light after completion of the study (for example, Rosenthal et al., 1984,1985a; Wirz-Justice et al., 1986) with a finding of repeated improvement provided the treatment was not withdrawn.

5. A placebo response is a major rival explanation for the antidepressant response found in most studies. However, it has been noted that "... placebo effects are more evident in mild or neurotic depressions..." (Wirz-Justice et al., 1986, p.201). Most subjects have been moderately to severely depressed and are not neurotic.

6. The finding that light exposed to the eyes has an antidepressant effect in seasonal depression whereas exposure to the skin does not (Wehr et al., 1987) is consistent with the idea that phototherapy is mediated by the retina. This appears to support the proposition that light acts via the retinohypothalamic tract, possibly to correct underlying disturbances in the circadian system.

Although these findings provide some strong arguments for phototherapy as being an active treatment, firm conclusions regarding the effectiveness of phototherapy cannot be made at the present time. Further research is needed to separate possible treatment effects from non-specific effects which may be causing or contributing to the observed results. Clearly, future research must concentrate on maximising experimental control and minimizing placebo effects.

In view of the major limitations of previous studies it seems appropriate to recommend strategies for future research. This is perhaps best achieved through an illustrative study which could be implemented as a test of the efficacy of phototherapy in endogenous and seasonal depression.[1]

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[1] It was originally hoped that the results of a study based on this outline could be presented here. Some major problems in the implementation of the study made it impossible to do this in the limited time available.

Design

Inherent in the use of cross-over designs is the ability of subjects to discriminate the placebo from the treatment condition. Such studies cannot reliably control for placebo effects. Unlike previous studies which have generally exposed subjects to both dim and bright light, this design requires that subjects receive one treatment or the other. Incoming endogenous and seasonal subjects would be randomly assigned to either bright or dim light in a 2 (type of depression) x 2 (intensity of light) factorial design. Hence four groups of subjects are required.

This basic design could be expanded to test various models. For example, to test the photoperiodic model light would be given from 0600h to 0800h and 2000h to 2200h daily.[1] Testing of other models require expansion of the design and the addition of extra conditions. For example, the phase response curve model involves another variable, that is, time of exposure (morning or evening). This would involve a 2 (type of depression) x 2 (intensity of light) x 2 (time of day)[2] factorial design and a total of eight conditions. A similar design could be used as a test of the photon-counting hypothesis, the time of day being replaced by the duration of light.[3] In the latter case it is essential that the time of administration is kept constant over all conditions.

Studies of this type involve more subjects than previous studies in this area. Ideally, about ten subjects in each condition are required. As the number of conditions needed to test a particular theory increases, so does the number of subjects. In terms of subject availability, five subjects per condition may be a more realistic figure in studies which have more than four conditions.

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[1] Based on prior research, 0600h appear to be the best time for morning exposure since it reduces the likelihood of sleep deprivation. Furthermore, four hours per day is sufficient to simulate a spring photoperiod.

[2] Morning exposures would be from 0600h to 0800h with evening exposures from 2000 to 2200h, based on the phase response curve model.

[3] Suggested durations are half an hour and one hour based on Wirz-Justice et al. (1987).

In an experiment of this kind it is unlikely that the required number of subjects will present at the same time. Therefore subjects would be randomly assigned to conditions before they present. Subjects would then begin the experiment as they become available. Essentially, this means that the study could be run over a lengthy period of time if the required number of subjects are not available at any one time. Of course only a fixed period of time during the winter months could be used for experimentation.

Subjects

Subjects should preferably be selected from the psychiatric population. They would be located through psychiatric institutions via close liaison with mental health professionals aware of the criteria for inclusion in the study.

Subjects must meet the DSM-III criteria for Major Depressive Disorder with Melancholia or SAD (Rosenthal et al., 1984) and currently be in a winter depressive episode. Subjects must also be free from medication so that responses to treatment conditions are not confounded. If not already inpatients, subjects would require hospitalization for the duration of the study. This is crucial to future studies testing the phase response curve model or the photon-counting hypothesis so that subjects can be continuously monitored to ensure that bright light is avoided at other times of day.

Experimental Conditions

Experimentation would be conducted in windowless rooms, of similar size, or rooms able to be shielded from outside illumination. Observations would be made from an adjacent room to ensure that subjects eyes remained open. Seating would be at a fixed distance from the light and subjects would be asked to remain seated during exposures.

Subjects would be exposed to lighting schedules individually so as to avoid possible effects due to social interaction. To control for activity, each subject would be given a standardized task to do on each day of exposure. For example, an I.Q. test on day one, a performance test on day two, a

puzzle on day three and so on. The type of task given each day would be kept constant across all subjects.

As with any experiment one cannot control for all variables. Imposing task requirements during light exposures may also introduce confounding effects. Mood may be influenced by the type of task the subject is required to do. Subjects may feel more depressed if they perceive the task to be tedious, boring, or if unable to complete the task. Additionally, some subjects may be more influenced by the tasks than others thereby making it impossible to hold this factor constant across all subjects.

Procedure

Once a potential subject becomes available, he/she would be interviewed in order to confirm the diagnosis necessary for inclusion in the study. Baseline measures of depression would be gathered using the Beck Depression Inventory and the Hamilton Rating Scale.[1] Seasonal depressives would also be administered an atypical symptom scale which considers those symptoms of SAD not addressed by the Hamilton. Subjects would then be exposed to light according to the treatment conditions to which they were previously assigned. Exposure should be for at least seven consecutive days. Following each exposure subjects would be asked to rate their mood on a visual analogue scale in order to gauge daily changes in mood. Subjects would be rated on the Hamilton and the Beck following the last exposure and then again at a one week follow-up.

Measures of Circadian Rhythms

Added credence would be given to the study by including concurrent measures of circadian rhythms. This would involve obtaining a comparison group of healthy subjects willing to participate in the experimental programme. Extensive measures of these rhythms are needed before, during, and after light treatment in order to determine the degree and direction of the phase-shift under both bright and dim light. In this way it is also

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[1] Based on prior studies. Hamilton to be rated by two clinicians blind to the treatment conditions.

possible to study the relationship of the individual phases of each rhythm with respect to one another. One might expect to find an initial desynchronization of rhythms and resynchronization following light exposure and mood improvement.

Ethical Problems

This type of research poses a number of ethical problems. A serious problem is that subjects in the dim light condition are exposed to a treatment that is not expected to be effective. Subjects would require close monitoring to ensure that their condition does not markedly deteriorate. Since subjects are inpatients there would be ample opportunity for regular checks by nursing staff. Subjects would be informed that they can withdraw themselves (or the experimenter can decide to stop the study) at any time.[1]

It could be suggested that subjects in the dim light condition be invited to try bright light following completion of the study if this has proven effective for other groups. Also, subjects using bright lights during the study may wish to continue on. Some researchers (for example, Yerevanian et al., 1986) have found that a portable incandescent light source is effective, and relatively inexpensive. This could be a possibility for subjects own use on completion of the study.

A related ethical issue is whether subjects in the dim light condition are being deceived in being given a treatment which they think to be effective but which is not expected to lead to improvement. This is a difficult issue as subjects may actually improve merely by receiving the 'special treatment' attached to the experiment. Adequate briefing and debriefing is necessary in experiments such as this in which deceptions are involved.

Problems of Implementation

The design presented here could pose some problems with respect to the practical implementation of the study. If subjects are to be selected from the

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[1] Subjects would be withdrawn should they deteriorate substantially.

psychiatric population it may be difficult to obtain subjects who are not on medication. One way of dealing with this problem would be to offer phototherapy as an alternative to subjects who are currently not responding to medication or who do not wish to take medication. This would require some discussion with staff psychiatrists but may be a feasible option. Patients would need to be free from medication for at least two weeks prior to study. This method of obtaining subjects is not without problems as this means that subjects would effectively self-select.

Another problem is related to the availability of subjects corresponding to the required diagnostic criteria. It may take some time to obtain the subject numbers needed. Although the design allows for this, the time of year at which seasonal subjects can undergo experimentation is limited.

Advantages

A study conducted along these lines has a number of advantages over previous studies in this area. First, it allows for rigorous control over variables such as light intensity, duration, activity during exposure, and bright light outside exposures. Second, subjects believe that the light intensity to which they are exposed will be effective. Third, a study such as this, conducted in New Zealand, is not as likely to have the problems of publicity inherent in many other studies since phototherapy is generally not as well known here as in other parts of the world. Therefore it is less likely that subjects will have preconceived ideas about the treatment they receive. Also, the apparent lack of research regarding this treatment in New Zealand would make it highly unlikely that subjects would have prior experience with phototherapy.

Further Lines of Investigation

Rhythms in seasonal depressives have generally not been well researched. Temperature, cortisol, and melatonin rhythms require more study. Additionally, it would be useful to compare individual rhythms during remission as well as depressive episodes in both endogenous and seasonal types. Moreover, there is very little research to date which has administered

phototherapy to endogenous depressives. More research is needed to establish the effectiveness of phototherapy for this group.

The measurement of circadian rhythms may have important implications for future studies of phototherapy. Although there is presently no direct evidence that corrections in circadian rhythm function causes mood improvement, there does appear to be a relationship between phase-shifts in overt rhythms, the effects of light, and mood change. The relationship between these factors deserves further investigation. Furthermore, the identification of disturbed circadian rhythms may not only indicate suitability for phototherapy but may also be useful as a biological marker for some types of depression. Study of the circadian rhythms of endogenous and seasonal depressives suggests that these groups have different types of biological disturbances. Measures of circadian rhythms may be helpful in assessing the direction (that is, phase-advance or phase-delay) and the degree of disturbance. This could ultimately lead to the provision of some important guidelines for the administration of phototherapy with respect to the duration and timing of light.

Of the theories proposed to explain the corrective effect of light the phase response curve model appears to be the most theoretically sound. However, the predictions generated by this model require more extensive testing. If substantiated by future research this model could be used in conjunction with biological measures of circadian rhythms to precisely quantify circadian disturbances. Although patients may be categorized according to the direction of the disturbance on the basis of diagnosis, one would expect some inter-individual variation within disorders. Using the predictions set out by the phase response curve model, bright light could be used to shift rhythms to their exact (correct) phase position. Thus therapy could be individually tailored, according to the type of rhythm disturbance and the timing/duration of light needed to correct the rhythm.

All theories require further testing and theories need testing against each other in order to determine which treatment regimen is most likely to be effective. The finding that most theories are supported to some extent may imply that the antidepressant response may be due to a combination of factors: A minimum intensity of light, a minimum duration, and a certain

time period within which light can be administered may be required before the antidepressant response can occur. Although melatonin does not appear to directly cause depression, as suggested by the photoperiodic model and melatonin-suppression hypothesis, it may be useful as a biological marker for the effects of light.

Future studies of phototherapy should ensure careful assessment of patients who undergo light treatment. Previous studies have noted that some patients are particularly sensitive to light and show mood improvement even in response to dim light (Rosenthal et al., 1985b; Wirz-Justice et al., 1986). Theoretically, too much light could result in a switch to mania or hypomania in some bipolar patients. These patients may require light of lower intensity than others. Research in this area could also be expanded to develop measures which will distinguish these light-sensitive individuals from other patients. Self-report (questionnaire) as well as biological methods (measures of melatonin) could be used to screen individuals for possible sensitivity to light.

Further research into the usefulness of phototherapy may have important implications for the treatment of depression. Future confirmation that this treatment does reduce depressive symptoms through well controlled research could make phototherapy a relatively inexpensive alternative to pharmacological interventions which often produce undesirable side effects. Furthermore, if vulnerability to depression in SAD is caused by circadian rhythm sensitivity to seasonal changes, phototherapy may be attacking directly one of the causes of depression.

Speculations

Many questions regarding the etiologies of SAD and endogenous depression remain unanswered. Once again one turns to animal research for clues as to the origins of these disorders.

Studies show that an organism's endogenous circadian period is partly genetically determined and that it is possible through selective breeding to produce long or short circadian periods in some experimental animals (Wehr, 1982). A genetic factor has also been found both in Major Depressive

Disorder (Gershon, Nurnberger, Nadi, Berrittini and Goldin, 1983) and SAD (Rosenthal et al., 1984,1985a). In view of this one might speculate that in humans, like other animals, abnormally long (closer to 26-hours) and short (less than 24-hours) endogenous circadian periods are inherited. An abnormally long (manifested as phase-delayed rhythms) or short (manifested as phase-advanced rhythms) endogenous circadian period implies a disturbance in the primary circadian pacemaker, resulting in the failure to entrain the endogenous rhythm to the 24-hour light-dark cycle. Assuming this to be pathogenic for depression, bright light might work by re-setting the primary circadian pacemaker thereby synchronizing this oscillator, and the overt bodily rhythms it controls, to the environmental light-dark cycle.

The existence of short and long endogenous periods in endogenous and seasonal depressives, respectively, could be tested by placing these individuals in an environment free from time-cues and obtaining measures of free-running circadian rhythms. However, a genetic explanation for abnormal endogenous periods would be difficult to test experimentally.

Other reasons for this occurrence may be more conducive to research. Another possibility is that the primary circadian pacemaker controlling the circadian rhythms in endogenous and seasonal depressives is affected by endocrine disturbances, thus altering the endogenous circadian period. This view is consistent with findings of abnormalities in some hormone systems in endogenous depressives. In Chapter Four it was noted that during a depressive episode endogenous depressives generally demonstrate high levels of cortisol, low levels of melatonin, and abnormal responses to dexamethasone. The finding that similar disturbances are not present in seasonal depressives may also indicate that different biological systems are involved in the etiology of the two disorders.

If the origin of SAD lies with endocrine dysfunctions, what are the systems that might be implicated in this disorder? A notable feature of SAD is that women outnumber men by a ratio of four to one. Perhaps the dysfunction involves hormones which are more common to women. Estrogen, which has been noted to alter the endogenous circadian period in certain experimental animals (Morin, Fitzgerald and Zucker, 1977), is one possibility. Alternatively, one might hypothesize a dysfunction in the serotonergic

system. Serotonin is the biochemical precursor for the synthesis of melatonin. When light impinges on the retina noradrenaline is inhibited and this sets off a chain of chemical reactions leading to a decrease in serotonin. Serotonin has been detected in the hypothalamus of humans and has been found to vary with season, the lowest concentrations being reported in autumn and winter (Carlsson, Svennerholm and Winblad, 1980). There is some suggestion that the serotonergic system may mediate some depressive symptoms. For example changes in the ratio of cholinergic activity in relation to noradrenergic or serotonergic activity appears to be related to aspects of sleep disturbances noted in depression (Carroll, 1983). Furthermore, there is some suggestion that serotonin deficiency may be related to other symptoms that affect SAD patients such as carbohydrate cravings (Rosenthal et al., 1985a).

The danger with these speculations is that they appear to present a rather simplistic view of these disorders. This is probably far from the case. Most likely, endogenous and seasonal depression are the result of many complex interactions involving many biological systems. Disturbances in circadian rhythms and some hormones are probably the manifestations of these interactions. A great deal more intensive research is needed before the origins of these disorders will become evident.

Final Remarks

In summary, phototherapy is a treatment which deserves further investigation. The consistency of findings which report antidepressant effects in endogenous and seasonal depressives following bright light suggests this is a potential treatment for these individuals. Other lines of evidence including findings that bright light has the capacity to shift circadian rhythms and indications of a physiological pathway which mediates the effects of light also suggests that phototherapy may have a direct biological action. Serious methodological problems evident in many studies makes it difficult to draw firm conclusions regarding the effectiveness of this therapy from the current research. The major weakness of these studies lies in poor experimental design which, in most cases, has posed some major threats to internal validity thus increasing the likelihood of spontaneous remission and placebo

responses. If the efficacy of phototherapy is to be properly evaluated, the problems reported on in the present thesis must be avoided.

Some experimental weaknesses cannot be completely dealt with. The availability of suitable subjects almost precludes proper randomization procedures and means that subjects will, to some extent, self-select. Despite this, many of the problems apparent in studies of phototherapy can be eliminated. Better, controlled and more extensive research will determine the effectiveness of phototherapy and lead to clarification of the underlying reasons for the antidepressant effects reported in studies of phototherapy, enabling the existing theoretical positions to be properly tested.

REFERENCES

Abe, K., Kroning, J., Greer, M.A., & Critchlow, V. (1979). Effects of destruction of the suprachiasmatic nuclei on the circadian rhythms in plasma corticosterone, body temperature, feeding, and plasma thyrotropin. Neuroendocrinology, 29, 119-131.

American Psychiatric Association. (1980). Diagnostic and statistical manual of mental disorders (3rd ed.). Washington, DC: Author.

Arendt, J., Bojkowski, C., Folkard, S., Franey, C., Marks, V., Minors, D., Waterhouse, J., Wever, R.A., Wildgruber, C., & Wright, J. (1985). Some effects of melatonin and the control of its secretion in humans. In Ciba Foundation Symposium (Eds.), Photoperiodism, melatonin and the pineal (pp. 266-283). London: Pitman.

Aschoff, J. (1963). Comparative physiology: Diurnal rhythms. Annual Review of Physiology, 25, 581-600.

Aschoff, J. (1979). Circadian rhythms: General features and endocrinological aspects. In D.T. Krieger, (Ed.), Endocrine rhythms (pp. 79-94). New York: Raven.

Avery, D.H., Wildschiodtz, G., & Rafaelson, O. (1982). Nocturnal temperature in affective disorders. Journal of Affective Disorders, 4, 61-71.

Beck-Friis, J., Kjellman, B.F., Aperia, B., Unden, F., von Rosen, D., Ljunggren, J., & Wetterberg, L. (1985a). Serum melatonin in relation to clinical variables in patients with major depressive disorder and a hypothesis of a low melatonin syndrome. Acta Psychiatrica Scandinavia, 71, 319-330.

Beck-Friis, J., Ljunggren, J.G., Thoren, M., von Rosen, D., Kjellman, B.F., & Wetterberg, L. (1985b). Melatonin, cortisol, and ACTH in patients with major depressive disorder and healthy humans with special reference to the outcome of the dexamethasone suppression test. Psychoneuroendocrinology, 10, 173-186.

Beck-Friis, J., von Rosen, D., Kjellman, B.F., Ljunggren, J.G., & Wetterberg, L. (1984). Melatonin in relation to body measures, sex, age, season, and the use of drugs in patients with major affective disorders and healthy subjects. Psychoneuroendocrinology, 9, 261-227.

Beersma, D.G., van den Hoofdakker, R.H., & van Berkestijn, H.W. (1983). Circadian Rhythms in affective disorders: Body temperature and sleep physiology in endogenous depressives. Advances in Biological Psychiatry, 11, 114-127.

Bittman, E.L. (1985). The role of rhythms in response to melatonin. In Ciba Foundation Symposium (Eds.), Photoperiodism, melatonin and the pineal (pp. 149-169). London: Pitman.

Brown, F.M., & Graeber, R.C. (Eds.). (1982). Rhythmic aspects of behaviour. New Jersey: Erlbaum associates.

Brown, R.B., Kocsis, J.H., Caroff, S., Amsterdam, J., Winokur, A., Stokes, P.E., & Frazer, A. (1985). Differences in nocturnal melatonin secretion between melancholic depressed patients and control subjects. American Journal of Psychiatry, 142, 811-816.

Bunning, E. (1960). Biological clocks. Cold Spring Harbor Symposia in Quantitative Biology, 25, 1-10.

Bunning, E. (1964). The physiological clock. Berlin: Springer-Verlag.

Cahn, H.A., Folk, G.E., & Huston, P.E. (1968). Age comparison of human day-night physiological differences. Aerospace Medicine, 39, 608-610.

Carlsson, A., Svennerholm, L., & Winblad, B. (1980). Seasonal and circadian variations in human brains examined post-mortem. Acta Psychiatrica Scandinavia, 61, 75-85.

Carroll, B.J. (1983). Neurobiologic dimensions of depression and mania. In J. Angst (Ed.), The origins of depression: Current concepts and approaches (pp. 163-186). Berlin: Springer-Verlag.

Conroy, R.T., & Mills, J. (1970). Human circadian rhythms. London: Churchill.

Czeisler, C.A., Allan, J.S., Strogatz, S.H., Ronda, J.M., Sanchez, R., Rios, C.D., Freitag, W.O., Richardson, G.S., & Kronauer, R.E. (1986). Bright light resets the circadian pacemaker independent of the timing of the sleep-wake cycle. Science, 233, 667-671.

Czeisler, C.A., Richardson, G.S., Zimmerman, J.C., Moore-Ede, M.C., & Weitzman, E.D. (1981). Entrainment of human circadian rhythms by light-dark cycles: A reassessment. Photochemistry and Photobiology, 34, 239-247.

Czeisler, C.A., Zimmerman, J.C., Ronda, J.M., Moore-Ede, M.C., & Weitzman, E.D. (1980). Timing of REM sleep is coupled to the circadian rhythms of body temperature in man. Sleep, 2, 329-346.

Dement, W.C., & Kleitman, N. (1957). Cyclic variations in EEG during sleep and their relation to eye movements, body motility and dreaming. Electroencephalography and Clinical Neurophysiology, 9, 673-690.

Dietzel, M., Saletu, B., Lesh, O.M., Sieghart, M., & Schjerve, S. (1986). Light treatment in depressive illness. Polysomnographic, psychometric and neuroendocrinological findings. European Neurology, 25, 93-103.

Doerr, P., von Zerssen, D., Fischler, M., & Schultz, H. (1979). Relationship between mood changes and adrenal cortical activity in a patient with 48-hour unipolar depressive cycles. Journal of Affective Disorders, 1, 93-104.

Doig, R.J., Mummery, R.V., Wills, M.R., & Elkes, A. (1966). Plasma cortisol levels in depression. British Journal of Psychiatry, 112, 1263-1267.

Eastwood, M.R., & Stiasny, S. (1978). Psychiatric disorder, hospital admission and season. Archives of General Psychiatry, 35, 769-771.

Fullerton, D.T., Wenzel, F.J., Lohrenz, F.N., & Fahs, H. (1968). Circadian rhythm of adrenal cortical activity in depression. Archives of General Psychiatry, 19, 682-688.

Gershon, E.S., Nurnberger, J.I., Nadi, N.S., Berrittini, W.H., & Goldin, L.R. (1983). Current status of genetic research in affective disorders. In J. Angst (Ed.), The origins of depression: Current concepts and approaches (pp. 187-204). Berlin: Springer-Verlag.

Gresham, S.C., Agnew, W.F., & Williams, R.L. (1965). The sleep of depressed patients. Archives of General Psychiatry, 13, 503-507.

Gruber, C.M. (1956). Interpreting medical data. Archives of Internal Medicine, 98, 767-773.

Halbreich, U. (1984). Effect of age and sex on cortisol secretion in depressives and normals. Psychiatry Research, 13, 221-229.

Halberg, F. (1959). Physiologic 24-hour periodicity: General and procedural considerations with reference to the adrenal cycle. Vitamin-Hormon-Fermentforsch, 10, 225-296.

Hellekson, C.J., Kline, J.A., & Rosenthal, N.E. (1986). Phototherapy for seasonal affective disorder in Alaska. American Journal of Psychiatry, 143, 1035-1037.

Honma, K., Honma, S., & Wada, T. (1987). Entrainment of human circadian rhythms by artificial bright light cycles. Experientia, 43, 572-574.

Illnerova, H., Zvolsky, P., & Vanecek, J. (1985). The circadian rhythm in plasma melatonin concentration of the urbanized man: The effects of summer and winter time. Brain Research, 328, 186-189.

James, S.P., Wehr, T.A., Sack, D.A., Parry, B.L., & Rosenthal, N.E. (1985). Treatment of seasonal affective disorder with light in the evening. British Journal of Psychiatry, 147, 424-428.

Knapp, M.W., Keane, P.M., & Wright, J.G. (1967). Circadian rhythm of plasma 11-hydroxycorticosteroids in depressive illness, congestive heart failure and Cushing's syndrome. British Medical Journal, 2, 27-30.

Kneisley, L.W., Moskowitz, M.A., & Lynch, H.J. (1978). Cervical spinal cord lesions disrupt the rhythm in human melatonin excretion. Journal of Neural Transmission, 13, 311-320.

Kramer, B.A., & Katz, J.L. (1978). Circadian temperature variation and depressive illness. Journal of Clinical Psychiatry, 39, 439-444.

Krieger, D.T., & Rizzo, F. (1971). Circadian periodicity of plasma 11-hydroxycorticosteroid levels in subjects with partial and absent light perception. Neuroendocrinology, 8, 165-179.

Kripke, D.F., Risch, S.C., & Janowsky, D.S. (1983a). Bright white light alleviates depression. Psychiatry Research, 10, 105-112.

Kripke, D.F., Risch, S.C., & Janowsky, D.S. (1983b). Lighting up depression. Psychopharmacology Bulletin, 19, 526-530.

Kupfer, D.J. (1976). REM latency: A psychobiologic marker for primary depressive disease. Biological Psychiatry, 11, 159-174.

Kupfer, D.J., Foster, F.G., Coble, P.A., McPartland, R.J., & Ulrich, R.E. (1978). The application of EEG sleep for the differential diagnosis of affective disorders. American Journal of Psychiatry, 135, 387-396.

Kupfer, D.J., Shaw, D.H., Ulrich, R.E., Coble, P.A., & Spiker, D.G. (1982). Application of automated REM analysis in depression. Archives of General Psychiatry, 34, 569-573.

Lee, M.A., & Taylor, M.A. (1983). Cortisol suppression and circadian rhythm in endogenous depression: A preliminary report. Biological Psychiatry, 18, 1127-1132.

Lewy, A.J., Kern, H.A., Rosenthal, N.E., & Wehr, T.A. (1982). Bright artificial light treatment of a manic-depressive patient with a seasonal mood cycle. American Journal of Psychiatry, 139, 1496-1498.

Lewy, A.J., Nurnberger, J.I., Wehr, T.A., Pack, D., Becker, L.E., Powell, R-L., & Newsome, D.A. (1985). Supersensitivity to light: A possible trait marker for manic-depressive illness. American Journal of Psychiatry, 142, 725-727.

Lewy, A.J., Sack, R.L., Frederikson, R.H., Reaves, M., Denny, D.D., & Zielske, D.R. (1983). The use of bright light in the treatment of chronobiologic sleep and mood disorders: The phase response curve. Psychopharmacology Bulletin, 19, 523-525.

Lewy, A.J., Sack, R.L., Miller, L.S., & Hoban, T.M. (1987). Antidepressant and circadian phase shifting effects of light. Science, 235, 352-357.

Lewy A.J., Sack, R.L., & Singer, C.M. (1984). Assessment and treatment of chronobiologic disorders using plasma melatonin levels and bright light exposure: The clock-gate model and the phase response curve. Psychopharmacology Bulletin, 20, 561-565.

Lewy, A.J., Sack, R.L., & Singer, C.M. (1985). Treating phase typed chronobiologic sleep and mood disorders using appropriately timed bright artificial light. Psychopharmacology Bulletin, 21, 368-372.

Lewy, A.L., Wehr, T.A., Goodwin, F.K., Newsome, D.A., & Markey, S.P. (1980). Light suppresses melatonin secretion in humans. Science, 210, 1267-1269.

Lieberman, H.R., Garfield, G., Waldhauser, F., Lynch, H.J., & Wurtman R.J. (1985). Possible behavioural consequences of light-induced changes in melatonin availability. Annals of the New York Academy of Sciences, 453, 242-252.

Lobban, M.C. (1967). Daily rhythms of renal excretion in Arctic-dwelling Indians and Eskimos. Journal of Experimental Physiology, 52, 401-410.

Lobban, M.E. (1977). Seasonal changes in daily rhythms of renal excretion and activity patterns in an Arctic eskimo community. Journal of Interdisciplinary Cycle Research, 8, 259-263.

Lobban, M.C., & Tredre, B. (1964). Renal diurnal rhythms in blind subjects. Journal of Physiology, 170, 29-30.

Lydic, R., Schoene, W.C., Czeisler, C.A., & Moore-Ede, M.C. (1980). Suprachiasmatic region of the human hypothalamus - homolog to the primate circadian pacemaker. Sleep, 2, 355-361.

Maron, L., Rechtschaffen, A., & Wolpert, E.A. (1964). Sleep cycle during napping. Archives of General Psychiatry, 11, 503-598.

Mayer-Gross, M., Slater, E., & Roth, M. (1969). Clinical psychiatry. London: Bailiere, Tindall and Cassell.

Mendlewicz, J., Linkowski, P., Branchey, L., Weinberg, U., Weitzman, E.D., & Branchey, M. (1979). Abnormal 24-hour pattern of melatonin secretion in depression. The Lancet, 2, 1362.

Miles, L.E.M., Raynal, D.M., & Wilson, M.A. (1977). Blind man living in normal society has circadian rhythms of 24.9 hours. Science, 198, 421-423.

Minors, D.S., & Waterhouse, J.M. (1981). Circadian rhythms and the human. Bristol: John Wright and Sons Ltd.

Moore, R.Y., & Lenn, N.J. (1972). A retinohypothalamic projection in the rat. Journal of Comparative Neurology, 146, 1-9.

Moore, R.Y. (1973). Retinohypothalamic projection in mammals: A comparative study. Brain Research, 49, 403-409.

Moore, R.Y. (1978). Central neural control of circadian rhythms. In W.F Ganong & L. Martini (Eds.), Frontiers in neuroendocrinology (pp. 112-130). New York: Raven.

Moore-Ede, M.C. (1981). Light: An information source for circadian clocks. Photochemistry and Photobiology, 34, 237-238.

Morin, L.P., Fitzgerald, R.M., & Zucker, I. (1977). Estradiol shortens the period of hamster circadian rhythms. Science, 196, 305-307.

Mosko, S., & Moore, R.Y. (1979). Retinohypothalamic tract development-alteration by suprachiasmatic lesions in the neonatal rat. Brain Research, 164, 1-15.

Pflug, B., Erikson, R., & Johnsson, A. (1976). Depression and daily temperature: A long term study. Acta Psychiatrica Scandinavia, 54, 254-266.

Pflug, B., & Tolle, R. (1971). Disturbance of the 24-hour rhythm in endogenous depression and the treatment of endogenous depression by sleep deprivation. International Pharmacopsychiatry, 6, 187-196.

Pittendrigh, C.S. (1960). Circadian rhythms and circadian organization of living systems. Cold Spring Harbor Symposia in Quantitative Biology, 25, 159-182.

Rickels, K., Hesbacher, P.T., Weise, C.C., Gray, B., & Feldman, H.S. (1970). Pills and improvement: A study of placebo response in psychoneurotic outpatients. Psychopharmacologia, 16, 318-328.

Roelfsema, F. (1987). The influence of light on circadian rhythms. Experientia, 43, 7-13.

Rosenthal, N.E., Sack, D.A., Carpenter, C.J., Parry, B.L., Mendelson, W.B., & Wehr, T.A. (1985b). Antidepressant effects of light in seasonal affective disorder. American Journal of Psychiatry, 142, 163-170.

Rosenthal, N.E., Sack, D.A., Gillin, J.C., Lewy, A.J., Goodwin F.K., Davenport, Y., Mueller, P.S., Newsome, D.A., & Wehr, T.A. (1984). Seasonal affective disorder: A description of the syndrome and preliminary findings with light therapy. Archives of General Psychiatry, 41, 72-80.

Rosenthal, N.E., Sack, D.A., James, S.P., Parry, B.L., Mendelson, L.T., Tamarkin, L., & Wehr, T.A. (1985a). Seasonal affective disorder and phototherapy. Annals of the New York Academy of Sciences, 453, 260-269.

Rusak, B., & Boulos, Z. (1981). Pathways for photic entrainment of mammalian circadian rhythms. Photochemistry and Photobiology, 34, 267-273.

Rusak, B., & Groos, G. (1982). Suprachiasmatic stimulation phase-shifts rodents circadian rhythms. Science, 215, 1407-1409.

Sachar, E.J., Hellman, L., Roffwarg, H.P., Halpern, F.S., Fukushima, D.K., & Gallagher, T.F. (1973). Disrupted 24-hour patterns of cortisol secretion in psychotic depressives. Archives of General Psychiatry, 28, 19-24.

Schiligen, B., & Tolle, R. (1980). Partial sleep deprivation as therapy for depression. Archives of General Psychiatry, 37, 267-271.

Schulz, H., & Lund, R. (1983). Sleep onset REM episodes are associated with circadian pacemakers of body temperature: A study in depressed patients and normal controls. Biological Psychiatry, 18, 1441-1426.

Spitzer, R.L., Endicott, J., Robins, E. (1978). Research diagnostic criteria: Rationale and reliability. Archives of General Psychiatry, 35, 773-782.

Swanson, L.W., Cowan, W.M., & Jones, E.G. (1974). Autoradiographic study of efferent connections of ventral lateral geniculate nucleus in albino rat and cat. Journal of Comparative Neurology, 156, 143-163.

Symonds, R.L., & Williams, P. (1976). Seasonal variation in the incidence of mania. British Journal of Psychiatry, 129, 45-48.

Szafarczyk, A., Ixart, G., Malaval, F., Nouguier-Soule, J., & Assenmacher, I. (1979). Effects of lesions of the suprachiasmatic nuclei and of para-chlorophenylalanine on the circadian rhythms of adrenocorticotrophic hormone and corticosterone in the plasma, and on locomotor activity of rats. Journal of Endocrinology, 83, 1-16.

Takahashi, J.S., & Zatz, M. (1982). Regulation of circadian rhythmicity. Science, 217, 1104-1111.

Vaughnan, G.M., McDonald, S.D., Jordan, R.M., Allen, J.P., Bell, R., & Stevents, E.A. (1979). Melatonin, pituitary function, and stress in humans. Psychoneuroendocrinology, 4, 351-369.

Vogel, G.W., Vogel, F., McAbee, R.S., & Thurmond, A.J. (1980). Improvement of depression by REM sleep deprivation: New findings and a theory. Archives of General Psychiatry, 37, 247-253.

von Zerssen, D. (1983). Chronobiology of depression. In J. Angst (Ed.), The origins of depression: Current concepts and approaches (pp. 253-271). Berlin: Springer-Verlag.

Wehr, T.A. (1982). Circadian rhythm disturbances in depression and mania. In F.M Brown and R.C. Graeber (Eds.), Rhythmic aspects of behaviour (pp. 399-428). New Jersey: Erlbaum Associates.

Wehr, T.A., Jacobsen, F.M., Sack, D.A., Arendt, J., Tamarkin, L., & Rosenthal, N.E. (1986). Time of day and suppression of melatonin are not critical for antidepressant effects. Archives of General Psychiatry, 43, 870-875.

Wehr, T.A., Muscettola, G., & Goodwin, F K. (1980). Urinary 3-methoxy-4-hydroxy-phenylglycol circadian rhythm: Early timing (phase advance) in manic depressives compared with normal subjects. Archives of General Psychiatry, 37, 257-263.

Wehr, T.A., Skwerer, R.G., Jacobsen, F.M., Sack, D.A., & Rosenthal, N.E. (1987). Eye versus skin phototherapy of seasonal affective disorder. American Journal of Psychiatry, 144, 753-757.

Wetterberg, L. (1983). The relationship between the pineal gland and the pituitary-adrenal axis in health, endocrine, and psychiatric conditions. Psychoneuroendocrinology, 8, 75-80.

Wetterberg, L. (1985). Melatonin and affective disorders. In Ciba Foundation Symposium (Eds.), Photoperiodism, melatonin and the pineal, (pp. 253-278). London: Pitman.

Wetterberg, L., Aperia, B., & Beck-Friis, J. (1981). Pineal-hypothalamic-pituitary function in patients with depressive illness. In K. Fuxe (Ed.), Steroid hormone regulation of the brain (pp. 397-403). Oxford: Pergamon.

Wetterberg, L., Beck-Friis, J., Aperia, B., & Petterson, U. (1979). Melatonin/cortisol ratio in depression. The Lancet, 2, 1361.

Wever, R. (1970). Strength of a light-dark cycle as a zeitgeber for circadian rhythms in man. Pflugers Archives, 321, 133-142.

Wever, R. (1979). The circadian system of man: Results of experiments under temporal isolation. Berlin: Springer-Verlag.

Wever, R. (1981). Organization of the human circadian system: Internal interactions. In T.A. Wehr and F.K. Goodwin (Eds.), Circadian rhythms in psychiatry (pp. 58-64). Los Angeles: Boxwood Press.

Wever, R. (1982). Circadian behavioural rhythmicity. In F.M. Brown and R.C. Graeber (Eds.), Rhythmic aspects of behaviour (pp. 105-171). New Jersey: Erlbaum Associates.

Wever, R., Polasek, J., & Wildgruber, C.M. (1983). Bright light affects human circadian rhythms. Pflugers Archives, 396, 85-87.

Wirz-Justice, A., & Arendt, J. (1979). Diurnal, menstrual cycle and seasonal indole rhythms in man and their modification. In J. Obiols, G. Ballus, E. Gonzales-Monclus (Eds.), Biological psychiatry today (pp. 298-341). Amsterdam: Elsevier/North Holland.

Wirz-Justice, A., Bucheli, C., Graw, P., Kielholtz, P., Fisch, H-U., & Woggon, B. (1986). Light treatment of seasonal affective disorder in Switzerland. Acta Psychiatrica Scandinavia, 74, 193-204.

Wirz-Justice, Schmid, A.C., Graw, P., Krauchi, K., Kielholz, P., Poldinger, W., Fisch, H-U., & Buddeberg, C. (1987). Dose relationships of morning bright white light in seasonal affective disorders (SAD). Experientia, 43, 574-576.

Yerevanian, B.I., Anderson, J.L., Grota, L.J., Bray, M. (1986). Effects of bright incandescent light on seasonal and non-seasonal major depressive disorder. Psychiatry Research, 18, 355-364.

Zulley, J. (1980). Distribution of REM sleep in entrained 24-hour and free-running sleep-wake cycles. Sleep, 2, 377-389.