CHAPTER - II

REVIEW OF LITERATURE
THE REVIEW IS DIVIDED INTO THREE PARTS:

(1) NEUROANATOMY OF PINEAL GLAND

(2) SYNTHESIS OF MELATONIN & ITS USES

(3) PATIENTS WITH DEPRESSIVE EPISODE AND EFFECTS OF MELATONIN
NEUROANATOMY OF PINEAL GLAND

At various times in the history of medicine the precise function of the small discrete pea-like structure we have in the centre of our brains, called the pineal gland (corpus pineale), was considered to be: a memory valve, a valve controlling circulating vital fluids, the seat of the soul, and the site of a presumed pathology causing certain types of mental illness – “a stony hardness of the pineal gland” (McGillion, 1980). In the mid nineteen fifties this confusion began to clear when the pineal gland’s true function was discovered and the nature of the link between ourselves and certain events in the skies above us was finally revealed.

The modern systematic study of the pineal gland began in 1954 when, after a review of the existing literature, Kitay & Altschule (1954), suggested it could be a productive area for research. Their comprehensive review suggested that the gland – until then generally held to be unimportant by modern scientific medicine – appeared to have a number of possible, if minor, physiological roles, many of which had been reported in the literature on the light sensitivity of certain mammals (Fiske, 1941).

In humans, the pineal gland is 5 mm long, 1–4 mm thick and weighs about 100 mg, both in men and in women (Hasegawa et al, 1987). The size of the pineal gland is significantly smaller in patients younger than 2 years old than in older patients. The size of the pineal gland increases until 2 years of age and
remains stationary between the ages of 2 and 20 years. There is no difference in size between males and females (Sumida et al., 1996).

The pineal gland or epiphysis cerebri is a small grey organ occupying a depression between the superior colliculi. It is inferior to the splenium of corpus callosum, from which it is separated by the tela choroidea of third ventricle and contained cerebral vein (Standring, 2006).

Figure A: Human brain showing 'pineal gland'
Figure B: Pineal Gland (adult hindbrain and midbrain, postero-lateral view)
Figure C: Pineal Gland, Saggital section
The pineal gland is a central structure in the circadian system that is innervated by a neural multi-synaptic pathway originating in the suprachiasmatic nucleus (SCN) that is located in the anterior hypothalamus. The SCN is the major circadian pacemaker of the mammalian brain and plays a central role in the generation and regulation of biological rhythms (Swaab 2003 and Buijs et al., 2001). The pineal gland produces melatonin in a marked circadian fashion (Arendt, 1995), reflecting signals originating in the SCN. The human SCN innervates only a small number of hypothalamic nuclei directly (Dai et al., 1997 and Dai et al., 1998). However, it may impose circadian fluctuations indirectly on the organism by means of melatonin released from the pineal gland (Reiter, 1993c).

The pineal gland has a stalk which divides into two lamina. The ventral (or inferior) lamina is continuous with posterior commissure, and the dorsal (or superior) lamina is continuous with the habenular commissure. The extension of the cavity of third ventricle between the two laminae is termed as pineal recess. The pineal gland is innerveted by a nerve called nervus conarii which consists of postganglionic sympathetic fibers arising from superior cervical ganglion. The gland is a neuroendocrine gland and consists of parenchymal cells, called pinealocytes and neuroglial cells. The pinealocytes secrete a hormone called melatonin. The importance of the pineal gland lies in its function. In theoretical description formulated during the 1600s, R. Descartes described the pineal gland as the seat of soul. It is not for sure, a functionless vestigeal organ representing dorsal third eye (found in some types of fishes and amphibians) as was assumed in the recent
past. At present it is considered to be the most highly evolved gland of the body (Singh, 2005).

**The Yogic Chakra System:**

The yogic chakra system as explained by Swami Satyananda Saraswati (1972), consists of seven chakras which are normally depicted as a sort of “spinal column” with three channels called nadis (ida, pingala and sushumna) which interweave, the crossing-points being the sites of the chakras. In western terms this can be readily understood as the central nervous system (sushumna) in the spinal cord around which, on either side, runs the autonomic nervous system which has two aspects, the parasympathetic which can be readily correlated with ida, and the sympathetic with pingala, the sympathetic and pingala being the activating aspect of the system and the parasympathetic and ida the relaxing. Where these two cross they form plexuses, or nodes, from which nerves go out to, for example, the heart, lungs, diaphragm, digestive system and the endocrine organs. Satyananda connects this nervous system with the chakras.

These chakras are considered to be important points for the channelling of consciousness, energy nodes linking the physical with the spiritual. They have been adopted quite widely into popular usage in the West, partly through the Theosophists at the turn of the century, and partly because of the intense interest in Eastern spirituality birthed during the sixties. There are at present so many differing correspondences and attributes linked to them and therefore this research is presented with the aim of achieving greater clarity.
Table no. A : Correspondences popularly linked with chakras, Available from: URL: http://www.psi-researchcentre.co.uk/article_2.html

<table>
<thead>
<tr>
<th>Chakra</th>
<th>physiology</th>
<th>body</th>
<th>function</th>
<th>petals</th>
<th>colour</th>
<th>sense</th>
<th>motor</th>
<th>element</th>
<th>psychic experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sahasrara</td>
<td>crown</td>
<td>pituitary, brain</td>
<td>mind</td>
<td>1000</td>
<td>red</td>
<td>mind</td>
<td>mind</td>
<td>mind</td>
<td>red</td>
</tr>
<tr>
<td>Ajna</td>
<td>third eye</td>
<td>pineal</td>
<td>psychic awareness command</td>
<td>2</td>
<td>clear, grey</td>
<td>mind</td>
<td>mind</td>
<td>mind</td>
<td>Golden egg, drowsy</td>
</tr>
<tr>
<td>Vishuddhi</td>
<td>throat</td>
<td>laryngeal plexus</td>
<td>expression</td>
<td>16</td>
<td>pure blue</td>
<td>ears/hearing</td>
<td>vocal</td>
<td>ether</td>
<td>cold, nectar</td>
</tr>
<tr>
<td>Anahata</td>
<td>heard</td>
<td>cardiac plexus</td>
<td>love</td>
<td>12</td>
<td>Vermillion</td>
<td>Skin/touch</td>
<td>hand</td>
<td>air</td>
<td>blue</td>
</tr>
<tr>
<td>Manipura</td>
<td>navel</td>
<td>solar plexus</td>
<td>digestion, assimilation</td>
<td>10</td>
<td>dark blue</td>
<td>Eyes/sight</td>
<td>feet</td>
<td>fire</td>
<td>yellow</td>
</tr>
<tr>
<td>Swadhistana</td>
<td>Sacral</td>
<td>Prostatic plexus</td>
<td>The unconscious</td>
<td>6</td>
<td>Vermillion</td>
<td>Tongue/taste</td>
<td>Sex organs</td>
<td>Water</td>
<td>Unconscious</td>
</tr>
<tr>
<td>Muladhara</td>
<td>Perineum</td>
<td>Sacrococcygeal plexus</td>
<td>Excretory, secretory, sexual</td>
<td>4</td>
<td>red</td>
<td>nose/smell</td>
<td>Kidneys</td>
<td>Earth</td>
<td>Red</td>
</tr>
</tbody>
</table>
The Pineal Gland: Ajna Chakra:

All psychic systems have their physical aspects in the body with “ajna chakra”; the physical equivalent is the pineal gland, which has long baffled doctors and scientists as to its precise function. Yogis, who are scientists of the subtle mind, have always spoken of telepathy as a “siddhi”, a psychic power for thought communication and clairaudience, etc. The medium of such siddhis is ajna chakra, and its physical terminus is the pineal gland, which is connected to the brain. It has been stated by great yogis that the pineal gland is the receptor and sender of the subtle vibrations which carry thoughts and psychic phenomena throughout the cosmos.’ (Satyananda, 1972). Hence we have here a testable hypothesis formulated by a man who is knowledgeable not only in Eastern lore, but appears to have read Western scientific literature as well. Thus, folklore and yogic teaching suggest that the ‘third eye’ (pineal gland) plays some part in the process of becoming aware of psi information.

In recent years findings in neurochemistry and anthropology have given greater credence to the folklore which states that the pineal gland is the ‘third eye’, source of ‘second sight’, ‘seat of the soul’, or psychic centre within the brain (ajna chakra). In general the pineal is a very active organ, having the second highest blood flow after the kidneys and equal in volume to the pituitary. It has the highest absorption of phosphorus in the whole body and the second highest absorption of iodine, after the thyroid. No other part of the brain contains so much serotonin or is capable of making melatonin. A unique anatomical feature is that it is an unpaired midline organ in the brain which, alone of all equivalent organs, has resisted encroachment by the corpus callosum (Wiener, 1968; Quay, 1974)
Microanatomy:

On microscopic section the pineal gland is seen to be incompletely divided into lobules by connective tissue septa that extends into the substance of the gland from the capsule. Two types of cells are found in the gland, the pinealocytes and the glial cells. Concretions of calcified material called brain sand progressively accumulate within the pineal gland with age (Snell, 2006a).

Pinealocytes are not only the principal cellular components of the pineal gland, but they are also the principal synthetic machinery of this enigmatic gland with highly diverse and often questionable empyreal roles assigned to it. By ultrastructural descriptions of pinealocytes belonging to some 70 species of mammals (a mere 2% or less of the over 4,200 mammalian species) it can be summarized from the available literature with new observations on 12 species of chiropterans. A tabular listing of unusual structures reported within the pinealocyte cytoplasm points out the impending experimental work on these species. Such studies using the latest techniques might provide clearer insights into the functional role of the pineal gland as an important and integral component of the neuroendocrine axis. Whereas sufficient structural information now exists on cytoplasmic organelles such as synaptic ribbons and spherules, annulate lamellae, subsurface cisterns, and the several types of synaptic arrangements seen in relation to the pinealocyte soma and its processes, the functional role of these structures in pineal synthetic processes remains to be elucidated (Bhatnagar, 1990).
Figure D. Slide of pineal gland showing pinealocytes and astrocytes

The calcium phosphates and carbonates are deposited in the gland with age in the form of multilaminar corpuscles called corpora arenacia or brain sand (Singh, 2005).
Figure E: Slide of pineal gland showing ‘brain sand’

(corpora arenacia)

The pineal sand looks like ink spots which develops over time, so that older adults have considerably more than children (Wick, 1997).
It was soon established that the pineal gland produced a number of neuropeptides including one: 5-methoxy, N-acetyltryptamine, considered to be the most important of the pineal hormones and commonly called melatonin.

The biosynthesis of melatonin was discovered to be dependent on a number of substrates and co-factors, and on the activity of a number of enzymes including the light-sensitive: hydroxy-indole-O-methyl transferase (HIOMT) (Lerner et al, 1958; 1959).

The main environmental control of the pineal melatonin synthesis is light intensity. Light perceived by the retina reaches the supra chiasmatic nucleus (SCN) through the retinohypothalamic tract, which has been revealed by an in vitro postmortem tracing procedure, also in the human hypothalamus. The SCN innervates the pineal gland via the dorsomedial hypothalamic nucleus, the upper thoracic intermediolateral cell columns of the spinal cord and the superior cervical ganglia (SCG), resulting in the rhythmic secretion of melatonin (Ying-Hui Wu & Dick F. Swaab, 2004a).
As Brownstein and Heller (1968) demonstrated, this enzyme - which catalyses the conversion of serotonin to melatonin - is modulated by nerves that impinge directly onto the pineal gland, the activity of which, in turn, depend upon input from the optic nerves. Thus a small proportion of the impulses set up in the optic nerves bypasses the main visual pathway and, instead, takes a circuitous route to the pineal. Stimulation of these nerves increases the activity of HIOMT and, hence, stimulates the synthesis of melatonin. Bright light inhibits melatonin production by inhibiting nerve tone to the pineal, whereas darkness has the opposite effect and, by increasing neural activity to the gland, stimulates the production of melatonin. This effect of light is dependent both upon its wavelength and its intensity.

In 1973, Cardinali et al., showed that red light produced minimal inhibition of melatonin synthesis, whereas green light caused maximal stimulation. In addition, illumination with a light intensity of 0.5 microwatt/cm² for forty-eight hours produced a fifty per cent decrease in melatonin synthesis in the rat pineal gland.

By way of comparison, sunlight, which strongly inhibits melatonin production, has an intensity of around 50,000 microwatt/cm², whereas full moonlight has an intensity of around 0.3 microwatt/cm². (Altschule, 1975). Because of its low light intensity, the moon was originally thought to have no effect on the production of melatonin by the pineal gland. However, as we discuss below, more recent studies have produced results that suggest there may be some link between lunar phase and the secretion of melatonin (Law, 1986).

In addition to light, other electromagnetic (EM) radiations influence
related to the actual and putative effect(s) of melatonin on sexual development and hence to the effect of external EM radiation on the pineal gland. However, one action of extraneously administered melatonin on sexual development that was identified early on by researchers in this area, appeared not only to be related to its antigonadal action, but to be dependent upon the age of the recipient when it was administered, also.

"Pre-Programming" from Birth by Melatonin administration:

In a number of sophisticated studies of melatonin in animals, it appeared that, as with certain other hormones, the response of a neonatal animal to melatonin administration depended on precisely when the melatonin was administered in terms of chronological age. Thus it seemed that when melatonin was administered around the time of birth, it somehow produced changes in development that were delayed in onset until later in life and were therefore, in a biological sense, "pre-programmed".

Figure F: the "pre-programming" action of melatonin, Available from: URL:http://www.astrology-research.net/researchlibrary/latr/pineal.htm

(19)
Administration of melatonin to a neonate around the time of birth can cause developmental changes such as an inhibition or delay in the onset of secondary sexual characteristics. After a certain critical period post partum, however, - in rats six days - melatonin administration has no such effect.

Further, these effects, which have been replicated in contemporary studies, appeared to influence both normal and pathological development (Arai, 1968; Esquifino et al, 1987; Vaughan & Vaughan, 1974). It was also discovered that such changes in development did not take place if melatonin administration was delayed until a certain time after birth. Thus these delayed developmental effects of the hormone only occurred when it was administered at a set, critical time during the perinatal period. Such delayed-onset, or "pre-programming" effects of perinatally administered melatonin, while short lasting without reinforcement, were evident in a number of behavioural and physiological indices studied in animals, and they included, not only those associated with sexual development, but other developmental features also, including exploratory and maternal behaviour. Further, they could be produced either by the direct administration of melatonin, or by pinealectomy at birth, strongly suggesting a primary causal role for melatonin in these processes (Sampson, 1954; Sampson & Bigelow, 1971). In addition, observations in humans where congenital blindness, or exposure to extremes of light-dark periods had been evident at the time of, and immediately after, birth, paralleled these findings; and studies in both congenitally blind women and in other groups continue to provide pertinent observations and findings in this respect.
Effects of Ambient Electromagnetic Radiation in Melatonin production:

The production of melatonin is, amongst other things, controlled by the intensity and nature of ambient electromagnetic fields (EMFs) of geomagnetic strength, then the intensity and orientation of the EM fields a neonate is exposed to perinatally could obviously alter the level of pineal melatonin in that neonate and, hence, influence its later development. The exposure of neonatal animals to light significantly changes later melatonin secretion patterns, and that similar effects occur in human newborns (Fielke et al., 1994; Pelisek et al., 1994). As in animals, EM radiations significantly alter circulation melatonin in humans (Graham et al., 1997; Juutilainen et al., 2000; Reiter, 1995). There also appears to be a link between the geomagnetic field and developmental factors in humans. For example, the only significant factor that correlates with the development of epilepsy in young adults is the level of geomagnetic activity for two days after birth, and geomagnetic variables have also been considered to be a trigger for birth. There is also a significant correlation between the level of geomagnetism on, and for up to three days before, the birth of male children (Persinger & Hodge, 1999).

Wallace and Fisher (2001) have reported that our preference for day or night activity - i.e. whether we are a "day person" or a "night person" - appears to be determined quite simply by whether we were born during the day or born at night. The mechanism they suggest for this predisposition is one relating to a
setting of our body clock and, if true, the neonatal effects of melatonin and the light-dark sensitivity of the pineal gland could be important in this respect. Such an effect may also be related to season of birth. So, despite the many potential variables inherent in all these studies, what clearly emerges is the fact that the precise time of exposure to altered levels of melatonin, relative to the time of birth - is probably a critical factor in determining whether or not some change in development or behaviour is observed in adulthood. In other words, exposure of a neonate to melatonin, or to factors that significantly alter circulating melatonin levels at the time of birth - such as local geomagnetic and other EM fields - can potentially lead to highly significant changes in later development. Seasonal changes in melatonin levels that are directly associated with EMF intensity have been reported in the literature (Bergiannaki Joff et al, 1996), and this is suggestive of a possible linkage between: season, geomagnetic field fluctuation, melatonin production and immediate, or delayed, acute, or chronic, normal and pathophysiological states.

**Newborn and perturbations in electric and magnetic fields:**

In part as a consequence of the potential development-modifying actions of pineal activity and melatonin on neonates, Reiter (1995) has indicated that any perturbations in electric and magnetic fields that cause a reduction in normal melatonin levels in humans could have significant physiological and pathophysiological consequences. Such considerations have led some health professionals to re-assess the practice of exposing neonates in intensive care units and neonatal nurseries, to strong light and other EM fields, given the known,
or postulated association of such exposure with breast cancer, reproductive irregularities, and depression (Glottzbach et al, 1993).

**Biological function of melatonin:**

**Pineal gland as biological clock:**

The pineal gland functions as a biological clock by secreting melatonin (along with many other neuropeptides) at night. Melatonin levels peak at about 2 a.m. in normal, healthy young people and about 3 a.m. in elderly people. The maximum amount of melatonin released in the bloodstream of the elderly is only half of that in young adults. Melatonin levels are low during the day. At sunset, the cessation of light triggers neural signals which stimulate the pineal gland to begin releasing melatonin. This rise continues for hours, eventually peaking around 2 A.M. (3 A.M. for the elderly) after which it steadily declines to minimal levels by morning. The delay in timing and decrease in intensity of the melatonin pulse is a manifestation of the aging process (Dean et al, 2000).

The melatonin pulse regulates many neuroendocrine functions. When the timing or intensity of the melatonin peak is disrupted (as in aging, stress, jet-lag, or artificial jet-lag syndromes), many physiological and mental functions are adversely affected. The ability to think clearly, remember key facts, and make sound decisions can be profoundly hampered by these upsets in the biological clock.

(23)
Figure G: Rise of serum melatonin level in young and elderly, Available from: URL: http://www.ceri.com/melaton.htm
Figure H: Diagrammatic review of current hypothesis regarding the control and effects of pineal functions, Mary Dyson (1995), Endocrine system, Gray's Anatomy, 38th edition, P. 1890.
Melatonin for Jet-Lag:

Jet-lag is a condition caused by desynchronization of the biological clock. It is usually caused by drastically changing our sleep-wake cycle, as when crossing several time zones during east-west travel, or when performing shift work. Jet-lag is characterized by fatigue, early awakening or insomnia, headache, fuzzy thinking, irritability, constipation, and reduced immunity. The symptoms are generally worse when flying in an easterly direction, and it may take as long as one day for each time zone crossed in order to fully recover. Older people have an even tougher time adjusting to these changes than younger people. Circadian disturbances can easily result from conditions other than jet travel. We call these "artificial jet-lag syndromes" because jet-lag is universally understood. Artificial jet-lag can be induced by working night shifts, working rotating shifts (like physician-interns, management trainees for 24-hour businesses, and soldiers under battle-alert conditions), or by staying up all night. Whatever its causes, jet-lag and artificial jet-lag syndromes are seriously debilitating to cognitive function. Melatonin taken in the evening (in the new time zone!) will rapidly resets biological clock and almost totally alleviate (or prevent) the symptoms of jet-lag. The ability of melatonin to alleviate jet-lag was demonstrated in a study of 17 subjects flying from San Francisco to London (eight time zones away). Eight subjects took 5 mg of melatonin, while nine subjects took a placebo. Those who took melatonin had almost no symptoms of jet-lag (Arendt et al, 1986). Six out of nine placebo subjects scored above 50 on the jet lag scale, and all of the melatonin subjects scored below 17.
Figure I: Subjects taking Melatonin and Placebo in Jet-Lag, Available from: URL:http://www.ceri.com/melaton.htm
Melatonin improves mental performances:

With circadian enhancers like melatonin, the timing is critical. When taken in opposition to the body's natural circadian rhythm, they cause cognitive deficit just like jet-lag does. But when taken in synchronization with the body's natural circadian rhythms, they enhance mental performance. By giving melatonin in the daytime, before the cognitive tests, the researchers were causing the test subjects to suffer from artificial jet-lag and then measuring the resulting cognitive impairment. Disruption of circadian rhythms produces amnesia by interfering with the circadian organization of memory processes (Sandyk et al, 1991).

Melatonin, by correcting circadian rhythms should, theoretically, improve mental performance. One study was found where melatonin was given to rats at night. This study confirmed that next-day measures of learning ability improved (Ovanesov, 1990). Melatonin when taken before sleep, will decrease sleep disturbances of any kind, and will, therefore, improve mental function during the following day.

Melatonin for SAD and Depression:

Two particularly notable features of depression and SAD are diminished nighttime release of melatonin and abnormal sensitivity to melatonin suppression by light (Brown, 1989). This has led researchers and clinicians to try melatonin as an experimental treatment for depression, with gratifying results.
Melatonin Extends Lifespan:

Melatonin has also been shown to improve immunity and extend lifespan in rodents (Regelson & Pierpaoli, 1987; Pierpaoli, et al., 1990). Maestroni (1988) gave melatonin to middle-aged mice each evening. The treated mice became more healthy (better posture, increased activity levels, and thicker, more lustrous fur) and lived an average of 20% longer than control mice. Melatonin secretion naturally drops off with age. This decrease is so reliable that blood melatonin levels have been proposed as a measurement of biological age (Nair et al., 1986). This age-related reduction in melatonin levels may partially account for the reason many older people have difficulty sleeping at night, and for why they are so fatigued during the day. We can believe that they may be suffering from age-induced "jet-lag." Restoration of normal sleep-wake cycles in many elderly patients with supplemental melatonin before bedtime has dramatically improved their quality of life.
Figure J: Plasma melatonin in men and women, Available from:

URL: http://www.ceri.com/melaton.htm
Melatonin prevents aging and age related diseases:

According to Reiter (1995b), a prominent theory of aging attributes the rate of aging to accumulated free radical damage. Melatonin can markedly protect macromolecules, especially DNA, against free radical attack, it could, indeed, be a major factor in determining the rate at which organisms age. Besides its ability to directly scavenge the highly toxic hydroxyl radical, melatonin also promotes the activity of the antioxidative enzyme glutathione peroxidase, thereby further reducing oxidative damage. These actions may be manifested more obviously in the central nervous system, which is highly susceptible to damage by oxygen-based radicals and, because of its inability to regenerate and its high vulnerability to oxidative attack, its deterioration may be especially important in aging. Thus, if melatonin preferentially affords antioxidant protection to the brain, it could be a major player in delaying aging and age-related diseases. In the few studies where animals have been supplemented with exogenous melatonin throughout life, life span has been increased up to 25%. Besides its protection of the brain, melatonin has been shown to prevent damage by oxidants to DNA in other organs. Again, protecting DNA is particularly important because there are only two copies in each diploid cell, and structurally impaired DNA would not properly transcribe, leading to metabolic inefficiency and possibility to death of the cell. Thus, for a number of reasons, maintaining a robust melatonin rhythm by exogenously administering the indole may prove to have a variety of beneficial effects, which collectively could serve to prolong life, postpone aging, and reduce the chances of age-related diseases.

(31)
Melatonin as an antioxidant:

Melatonin is a highly important antioxidant. Free radicals are chemical constituents that have an unpaired electron. If an electron is added to O2 then the superoxide anion radical O2- is formed. O2- is reduced by superoxide dismutase to H2O2 which is toxic at high concentrations and can be reduced to OH. The hydroxyl radical (OH) damages cells. Melatonin is an efficient neutraliser of OH. (Reiter et al, 1995).

Age related brain deterioration is extremely costly in terms of quality of life. One of the potential major causes of age-related destruction of neuronal tissue is toxic free radicals that are a natural result of aerobic metabolism. The brain is particularly susceptible to free radical attack (Reiter, 1995c).

Vitamin antioxidants. Vitamin E (alpha-tocopherol in particular) and vitamin C (ascorbate) aid in protecting the brain from oxidative stress by directly scavenging toxic radicals. The pineal hormone melatonin is rapidly taken up by the brain. In vitro melatonin is more effective than glutathione in scavenging the highly toxic (OH) radical and also more efficient than vitamin E in neutralising the peroxyl radical. It also stimulates the main antioxidant enzyme of the brain, glutathione peroxidase. In vivo melatonin is a potent antioxidant (Goldman, 1995).
DEPRESSIVE EPISODE AND MELATONIN

F32 Depressive Episode:

As described by Philip W. Long, in typical depressive episodes (mild, moderate, and severe), the individual usually suffers from depressed mood, loss of interest and enjoyment, and reduced energy leading to increased fatiguability and diminished activity. Marked tiredness after only slight effort is common. Other common symptoms are:

(a) reduced concentration and attention;
(b) reduced self-esteem and self-confidence;
(c) ideas of guilt and unworthiness (even in a mild type of episode);
(d) bleak and pessimistic views of the future;
(e) ideas or acts of self-harm or suicide;
(f) disturbed sleep;
(g) diminished appetite.

The lowered mood varies little from day to day, and is often unresponsive to circumstances, yet may show a characteristic diurnal variation as the day goes on. As with manic episodes, the clinical presentation shows marked individual variations, and atypical presentations are particularly common in adolescence. In some cases, anxiety, distress, and motor agitation may be more prominent at times than the depression, and the mood change may also be masked by added features such as irritability, excessive consumption of alcohol, histrionic behaviour, and exacerbation of pre-existing phobic or obsessional symptoms, or by...
hypochondriacal preoccupations. For depressive episodes of all three grades of severity, a duration of at least 2 weeks is usually required for diagnosis, but shorter periods may be reasonable if symptoms are unusually severe and of rapid onset.

Some of the above symptoms may be marked and develop characteristic features that are widely regarded as having special clinical significance. The most typical examples of these "somatic" symptoms are: loss of interest or pleasure in activities that are normally enjoyable; lack of emotional reactivity to normally pleasurable surroundings and events; waking in the morning 2 hours or more before the usual time; depression worse in the morning; objective evidence of definite psychomotor retardation or agitation (remarked on or reported by other people); marked loss of appetite; weight loss (often defined as 5% or more of body weight in the past month); marked loss of libido. Usually, this somatic syndrome is not regarded as present unless about four of these symptoms are definitely present.

The categories of mild, moderate and severe depressive episodes described in more detail below should be used only for a single (first) depressive episode. Further depressive episodes should be classified under one of the subdivisions of recurrent depressive disorder.

These grades of severity are specified to cover a wide range of clinical states that are encountered in different types of psychiatric practice. Individuals with mild depressive episodes are common in primary care and general medical settings, whereas psychiatric inpatient units deal largely with patients suffering from the severe grades.

Acts of self-harm associated with mood (affective) disorders, most
commonly self-poisoning by prescribed medication, should be recorded by means of an additional code from Chapter XX of ICD-10 (X60-X84). These codes do not involve differentiation between attempted suicide and "parasuicide", since both are included in the general category of self-harm.

Differentiation between mild, moderate, and severe depressive episodes rests upon a complicated clinical judgement that involves the number, type, and severity of symptoms present. The extent of ordinary social and work activities is often a useful general guide to the likely degree of severity of the episode, but individual, social, and cultural influences that disrupt a smooth relationship between severity of symptoms and social performance are sufficiently common and powerful to make it unwise to include social performance amongst the essential criteria of severity.

The presence of dementia or mental retardation does not rule out the diagnosis of a treatable depressive episode, but communication difficulties are likely to make it necessary to rely more than usual for the diagnosis upon objectively observed somatic symptoms, such as psychomotor retardation, loss of appetite and weight, and sleep disturbance.

**F32.2 Severe Depressive Episode Without Psychotic Symptoms** :

In a severe depressive episode, the sufferer usually shows considerable distress or agitation, unless retardation is a marked feature. Loss of self-esteem or feelings of uselessness or guilt are likely to be prominent, and suicide is a distinct danger in particularly severe cases. It is presumed here that the somatic syndrome will almost always be present in a severe depressive episode.
Diagnostic Guidelines:

All three of the typical symptoms noted for mild and moderate depressive episodes should be present, plus at least four other symptoms, some of which should be of severe intensity. However, if important symptoms such as agitation or retardation are marked, the patient may be unwilling or unable to describe many symptoms in detail. An overall grading of severe episode may still be justified in such instances. The depressive episode should usually last at least 2 weeks, but if the symptoms are particularly severe and of very rapid onset, it may be justified to make this diagnosis after less than 2 weeks.

During a severe depressive episode it is very unlikely that the sufferer will be able to continue with social, work, or domestic activities, except to a very limited extent.

This category should be used only for single episodes of severe depression without psychotic symptoms; for further episodes, a subcategory of recurrent depressive disorder should be used.

Includes:

* single episodes of agitated depression
* melancholia or vital depression without psychotic symptoms

F32.3 Severe Depressive Episode With Psychotic Symptoms:

Diagnostic Guidelines:

A severe depressive episode which meets the criteria given for severe depressive episode without psychotic symptoms and in which delusions,
hallucinations, or depressive stupor are present. The delusions usually involve ideas of sin, poverty, or imminent disasters, responsibility for which may be assumed by the patient. Auditory or olfactory hallucinations are usually of defamatory or accusatory voices or of rotting filth or decomposing flesh. Severe psychomotor retardation may progress to stupor. If required, delusions or hallucinations may be specified as mood-congruent or mood-incongruent.

**Differential Diagnosis:**

Depressive stupor must be differentiated from catatonic schizophrenia, from dissociative stupor, and from organic forms of stupor. This category should be used only for single episodes of severe depression with psychotic symptoms; for further episodes a subcategory of recurrent depressive disorder should be used.

**Includes:**

* single episodes of major depression with psychotic symptoms, psychotic depression, psychogenic depressive psychosis, reactive depressive psychosis.

Beck-Friis et al (1985) studied the maximum nocturnal serum melatonin level (MTmax) in relation to some clinical variables in 32 patients with a major depressive episode and in 33 healthy subjects with reference to the outcome of the dexamethasone suppression test (DST). Significant regressions were found between maximum nocturnal serum melatonin levels and clinical rating scores, interpreted as retardation symptoms. Four healthy subjects with disposition for dysthymic reactions had subnormal maximum nocturnal serum
melatonin levels, which differed from maximum nocturnal serum melatonin levels in subjects without such disposition. Patients who reported parental loss of subnormal maximum nocturnal serum melatonin level differed from patients with no report of parental loss. Patients with no reported suicidal behaviour in clinical history had significantly lower maximum nocturnal serum melatonin levels than patients with reported suicide attempts. No relations were found between low maximum nocturnal serum melatonin levels and diagnoses, duration of illness, reported inheritance for depressive illness or sleep disturbances. A hypothetical low melatonin syndrome in depression is proposed:

1) low nocturnal melatonin,
2) abnormal dexamethasone suppression test,
3) disturbed 24-h rhythm of cortisol,
4) less pronounced daily and annual cyclic variation in depressive symptomatology.

Slow-release melatonin was effective in improving the sleep of patients with major depressive disorder. Slow-release melatonin had no effect on the rate of improvement in symptoms of major depressive disorder (Ornah et al, 1998). The authors conclude that the role of slow-release melatonin for sleep disturbances in major depressive disorder should be investigated further.

Melatonin may be combined with valproate to reduce the effective antiepileptic dose of the latter; the combination also possesses significant antidepressant activity (Siddiqui et al, 2001).

Depression can be associated with neuroendocrine and sleep abnormalities, such as reduced time before dream sleep (REM latency).
Melatonin has been suggested for the improvement of sleep patterns in patients with depression, although research is limited in this area (deVries et al, 1997, Dolberg et al, 1998, Dalton et al, 2000, Kripke et al, 2003). Further studies are needed before a clear conclusion can be reached.

Low nocturnal Melatonin has been proposed as a trait marker for major depressive disorders by Beck-Friis et al, 1985 (Webb and Puig-Domingo, 1995).

But in contrast to the previous literature, nocturnal melatonin secretion was not lower in the depressed group than in the normal group, and there was no difference in the timing of secretion; indeed, the trend was for greater melatonin secretion in the depressed group. The results are discussed in relation to previous studies, none of which has been so carefully controlled for the relevant variations (Thompson et al, 1988).

A recent study of postmenopausal women found that melatonin alleviated both depression and anxiety. Other studies show that people who suffer from major depression or panic disorder have low levels of melatonin. Healthy individuals with mild episodic depression and patients who have Seasonal Affective Disorder, (SAD -- a mild depression that correlates with fall and winter -- periods of light-phase shortening) also have lower than normal melatonin levels. Experimental studies show that melatonin causes a surge in the chemical serotonin, which helps alleviate symptoms of depressive illness, including major and mild depression and SAD. Melatonin should be used with caution in people with depression and should be appropriately timed with light therapy and sleep-phase changes. Disruption of normal circadian rhythm by poorly timed melatonin administration may worsen depression (American Accreditation HealthCare Commission, 2008).