

## Sleep, Sleep Deprivation, Sleeplessness and their Effect on Society

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### Abstract

### Review Article

Sleep is one of the attributes of wellness that needs further research and is often neglected in all disciplines of medicine except Psychiatry. The important aspects of sleep are Rapid Eye movement (REM) sleep, Non- Rapid Eye Movement (NREM) sleep and Dreaming. This review mentions the fundamental processes of sleep, the causes of sleep deprivation and dreaming. The physiological changes that occur through sleep are discussed along with medications aids in sleeping and the substances that affect or change the sleep pattern. The common factors associated with sleeplessness are emotional or mental tension, anxiety, depression, work problems, and an unsatisfactory sex life. Sleep medicine as a recent branch of medicine is reviewed as well as the use of Plant Medicine to deal with sleep disorders. Common substances used to induce sleep are hypnotic sedatives, and over the counter medications such as Benadryl and Nyquil. Alcohol is also used as a sleep aid. Herbal medicines are also commonly used as sleep aids. How sleep medication affects then biological pathways of man is emphasized (The Biochemistry of Sleep). Two hypothetical enzymes are proposed for the Biochemical Pathway starting with tryptophan and terminating in melatonin, a known sleep hormone. The two hypothetical enzymes proposed are 5-hydroxytryptophan synthetase and 5-hydroxytryptophan decarboxylase. The major problems associated with insufficient in the society is explained as well as the causes of sleep deprivation in this modern civilization. Some of the behavioral changes in the society that have contributed to sleep problems are shift work, increased work hours and extensive socialization.

**Keywords:** sleep, Sleep Medicine, Rapid Eye Movement (REM) sleep, Non-Rapid Eye Movement (NREM) sleep, Dreaming, Sleep biochemistry, hypothetical, Society, Sleep Medicine.

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## INTRODUCTION

There are eight dimensions of wellness as defined by SAMHSA Wellness Institute, Rockville, MD 20857.

1. Emotional-coping effectively with life and creating satisfying relationships.
2. Financial-satisfaction with current and future financial situations.
3. Social-developing a sense of connection, belonging, and a well support system.
4. Spiritual-expanding our sense of purpose and meaning in life.
5. Occupational –personal satisfaction and enrichment derived from one's work.
6. Physical- recognition of the need for physical activity, diet, sleep and nutrition.
7. Intellectual-recognizing creative abilities and finding ways to expand knowledge and skills.
8. Environmental- good health by occupying pleasant stimulating environments that support well-being.

This review focuses on Sleep, one of the physical attributes of wellness.

## Historical Background

French scientist Henri Pieron authored a book in 1913 which examined sleep from a physiological perspective. His work is usually regarded as the beginning of the modern approach to sleep research. In the 1920s Dr. Nathaniel Kleitman, known to date as the father of American Sleep Research began questioning the regulation of sleep and wakefulness and the circadian rhythms. Kleitman's work included sleep characteristics in different populations and the effect of Sleep Deprivation. In 1953 Kleitman and his student, Dr. Eugene Aserinsky, discovered the rapid eye movement (REM) during sleep.

Dr. William C. Dement, another one of Dr. Kleitman's students described the "cyclical" nature of nocturnal sleep in 1955. In 1957 and 1958 Dr. Dement established the relationship between REM sleep and dreaming. Dr. Dement published a paper in 1958 on the existence of a cyclic organization of sleep in cats. His findings of the sleep cycles in species other than humans created an explosion of research that involved

researchers from different fields such as electrophysiology, pharmacology and biochemistry. This impetus leads to Michael Jouvet's identification of REM sleep as an independent state of alertness, which he called paradoxical sleep. In Europe (1965) H. Gastaut and his colleagues made discoveries of apnea during sleep in a subgroup of Pickwickian patients that led to a flurry of investigations of the control exercised by the sleeping brain on the body's vital functions. This type of research led to a new discipline called Sleep Medicine.

To date, sleep research involves different areas such as narcolepsy research, sleep and cardio-respiratory research, studies on pain and sleep, circadian rhythms, sleep deprivation, sleep and aging, infant sleep, sleep medicine and the biochemistry of sleep.

There are over 200 accredited sleep disorder centers and laboratories in the United States of America alone, designed to treat all disorders of sleep. The Stanford Sleep Research Center was established by Dr. Dement in the 1970s and continues to be one of the leading Sleep Research Centers of the world. Sleep Research at the University of Chicago is also recognized worldwide.

## Sleep

Sleep is a fundamental anabolic process common to all living organisms. Sleep is recognizable by its contrast to wakefulness [1]. It is a state of reduced awareness and responsiveness to both internal and external stimuli [1]. The reduced awareness to stimuli is selective [2]. Sleep is an active process in which the significance of stimuli to the individual is interpreted and this determines whether arousal from sleep occurs [3]. In its heightened anabolic state sleep accentuates growth and rejuvenation of the immune, nervous, skeletal and muscular systems [4]. Sleep is observed in mammals, birds, fish, reptiles and amphibians [1, 5- 9].

For each species there is a particular posture or type of movement adopted during sleep [1]. Humans lie down, birds perch while asleep, horses may stand. Vampire bats sleep upside down, dolphins and whales swim, and albatrosses can fly [1]. In contrast to humans, sleep in some animals is not accompanied by physical activity [1]. Humans normally sleep with their eyes closed while some animals such as cattle and sheep sleep with their eyes open [1].

There are basically two kinds of sleep, namely, Rapid Eye Movement (REM) sleep, and Non-rapid Eye Movement (NREM) sleep or a non-dream sleep [10, 8, 11, 12]. During REM sleep a person shows rapid eye movements and the eye lids will move as though the individual is watching a movie [9]. REM sleep was first discovered in 1952 by Eugene Aserinsky, a graduate student who was monitoring a sleep experiment in the

laboratory of Nathaniel Kleitman at the University of Chicago [13]. William Dement was also working on the experiment. In 1962 Dement, Fisher and Rechtschaffen discovered the special pattern of REM sleep that onset in narcoleptics [14, 15]. These two discoveries transformed the understanding of narcolepsy etiology from a psychological basis to a physiological or neurophysiological one [9]. The diagnosis of narcolepsy became consolidated when an abnormality of REM sleep appeared on polysomnographic or brain wave testing [9]. This kind of testing records Electroencephalographic activity (EEG) or brain activity, Electroculographic activity (EOG) or eye movement, and Electromyographic activity (EMG) or muscular activity.

REM sleep is correlated to such physiological activities as inhibited or paralyzed movement, dreaming, changes in blood pressure, heart rate, high brain (cortical and cerebral) activity, intense inhibition and slightly reduced metabolic rate [8, 10, 12, 16, 11, 3]. Dement in 1972 indicated that without inhibition accompanying REM, dreaming individuals would constantly leap out of bed because of this high brain activity. REM sleep accounts for about 20% of the total sleep time in humans [11]. REM sleep produced the greatest number and reported intensity of dream reports [12]. Advances in neuroimaging techniques including functional magnetic resonance imaging (fMRI) and electromagnetic source localization are providing new details on the tonic conditions and phase neural events during REM that may contribute to the dream experience [12]. After the discovery of REM sleep, there was wide speculation that this sleep state, in which high and mixed frequency low amplitude Electroencephalogram (EEG) activity resembles waking, was the unique substrate of dreaming [17]. Although REM sleep produced dream reports following a high percentage of sleep laboratory sleep awakenings, when awakenings were performed from other sleep stages dreams were also reported [18]. REM reports are more visually vivid, motorically animated and emotional, and contain a higher amount of bizarre features [19]. REM appears to involve a reversion to a poikilothermic state and although brain temperature rises during REM thermoregulatory responses such as sweating and panting do not occur during REM [11]. REM is associated with events such as muscle twitches (middle ear muscles, legs, arms, and selected facial muscles), penile erections, and temporary paralysis of jaw, neck and limbs [11].

In humans, sleep is composed of four "descending" stages (REM and NREM), with stage 3 in NREM exhibiting slow wave sleep (SWS) [11]. The initiation of NREM sleep is gradual and is characterized by slowing of the EEG [11]. The American Academy of Sleep Medicine (AASM) divided NREM into three stages, N1, N2, and N3. (20). According to Siber and his colleagues (2007) N1 is the stage between sleep and

wakefulness. It is associated with active muscles, and the eyes roll slowly, opening and closing moderately. N2 is associated with theta activity and in this stage it is gradually harder to awaken the sleeper. In N2 the alpha waves of the previous stage are interrupted by abrupt activity called Sleep Spindles and K-complexes [21]. NREM-3 (N3) was formally divided into stages 3 and 4, and is now called Slow Wave Sleep (SWS) [20]. The SWS is initiated in the preoptic area and consists of delta activity, and high amplitude waves at less than 3.5 Hz [20]. The sleeper is less responsive to the environment and many environmental stimuli no longer produce any reactions [21].

Sleep proceeds in cycles of REM and NREM [11]. There are normally four or five sleep cycles per night. The order normally being NREM-1 (N1) --- NREM-2 (N2)—NREM-3 (N3) ----NREM-2(N2) --- REM [20]. There is a greater amount of deep sleep NREM-3 (N3) earlier in the night, while the proportion of REM sleep increases in two cycles before natural awakening [20, 21]. Both NREM and REM sleep appear to be involved in consolidating memory, but they have different influences [1]. Retention is best if stage 3 (NREM -3(N3) sleep in the first two hours of the night is followed by REM sleep in the last 25% of the night [1]. The sequence of NREM and REM sleep appear to be important [1]. Recall of cognitive procedures is better if there is a sequence of NREM and then REM sleep, but declarative memory appears not to require REM sleep [22]. Probabilistic learning, in which associations are made according to the likelihood of events being related, improves after sleep on the first night after the experience [1]. Declarative memory during sleep may be related to spindle activity in stage 2 (NREM-2) (N2) [23].

The thalamocortical pathways synchronize cortical activity, particularly during the sleep stages of NREM [3]. The synchronization of cortical activity is not homogenous [3]. Early REM sleep is most marked in the prefrontal area, suggesting that this region, which is particularly active during wakefulness, develops a greater homeostatic drive and enters NREM sleep [3]. This region is difference is particularly marked after sleep deprivation [3]. NREM sleep affects Electroencephalogram (EEG) activity, mental activity, motor activity, autonomic function, metabolic rate, temperature control, gastrointestinal function, genitourinary function, endocrine function, and immunological function [3]. The three stages of NREM sleep are recognizable and quantifiable on the conventional EEG criteria. They are categorized by frequency and amplitude of the EEG, the presence of sleep spindles and K-complexes, and electrooculogram (EOG) and Electromyogram (EMG) findings. Individuals awoken during NREM sleep frequently report awareness of fragmented, thought like processes particularly in the lighter stages and later in the night.

During NREM sleep motor activity such as the reflex activity is depressed resulting in the reduction of the tendon reflexes, and in 50% of the tested individuals there is an upgoing planar (BaBinski) reflex [3]. The parasympathetic activity is also increased during NREM sleep due to the circadian factors at night. In contrast, the sympathetic system is more influenced by the sleep wake state than the circadian rhythms. The parasympathetic activity increases from stages 1 through 3 of NREM sleep, and the balance of parasympathetic to sympathetic activity remain stable. The metabolic rate is reduced by 5-10% in NREM sleep.

The core temperature of the body normally falls as NREM sleep is entered at the start of the night, and the control of sleep is closely related to thermoregulation. The reduced metabolic rate and Vasodilatation of NREM sleep tend to reduce body temperature [3]. The stage of NREM sleep oscillates frequently at the onset of sleep and the threshold for carbon dioxide to act as a respiratory stimulus fluctuates correspondingly. Within each stage of NREM sleep the respiratory pattern is regular, but it varies between stages as the threshold for responding to Pco2 (apnoeic threshold) alters. The activity of the chest wall muscles is globally reduced in NREM, unlike REM sleep in which the diaphragm is selectively spared, so that the ratio of rib cage to abdominal movement is greater in NREM than REM sleep [3]. There is a reduction in respiratory activity in NREM sleep which parallels the reduced requirements needed to cope with lower metabolic rate.

The cardiovascular system is more stable NREM sleep than REM sleep [3]. The heart rate falls shortly after sleep onset, and there is then little further change between stages 2, and 3 of NREM sleep, although it continues to fall during the night because of circadian rhythms. The blood pressure is not under circadian control, but is more sleep rate dependent [3]. The blood pressure falls by 5-15% shortly after sleep onset due mainly to the reduction of cardiac output, but also to peripheral vasodilatation. There is little difference between either the systolic or diastolic blood pressure in stages 2 and 3 of NREM sleep. The cerebral blood flow falls by 10-20% in NREM sleep as compared to wakefulness, and less than during REM sleep. The cutaneous blood flow is increased due to vasodilatation, but there is probably little change in the distribution of visceral blood flow during NREM sleep [3].

Less saliva is produced during sleep than during wakefulness, but the volume is similar in NREM and REM sleep. The sensation of a dry mouth is common during sleep, particularly in the presence of snoring and sleep apneas [3]. The swallowing frequency is similar during wakefulness in Stage 1 NREM sleep, but in deeper stages it is less frequent [3]. There are

rhythmic gastric contractions approximately every 20 seconds in NREM sleep [3]. Changes in the stability of the anal sphincter have been found during sleep [3].

There is wide diurnal variation in renal function. Water and sodium are retained at night and of the 1-2 liters of urine that is normally excreted in a 24 hour period, around 80% is produced during the day [3]. There is considerable change in the endocrine function during NREM sleep compared to wakefulness [3]. The changes in the immune function in sleep are not well documented, but the blood eosinophil and cortisol levels, and the natural killer (NK) cell activity fluctuate with a circadian pattern [3]. A relationship exists between melatonin, cytokines, and interferon, all of which have immunological actions, and influence sleep. The T-lymphocyte level rises in sleep, but the peripheral blood monocyte concentration falls, largely because the cells are sequestered in the spleen [3].

Dreaming is the perceived experience of sensory images and sounds during sleep, in a sequence which the dreamer normally perceives more as an apparent participant than as an observer. Dreaming is stimulated by the pons and mostly occurs during the REM phase of sleep. When individuals are awakened from REM, they generally report a narrative involving the dreamer, with vivid visual detail, unpleasant emotions, and occasional bizarre and improbable events [11, 19]. A meta-analysis of 29 awakenings revealed that about 82% of the awakenings from REM result in recall of a dream, whereas this frequency following NREM awakenings is lowered to 42% [24]. Dreams can also be suppressed or encouraged. Taking antidepressants, acetaminophen, ibuprofen, or alcohol is thought to suppress dreams, whereas melatonin may have the ability to encourage them [25].

There are many postulated hypotheses about the functions of dreaming. Sigmund Freud postulated that dreams are the symbolic expression of frustrated desires that have been regulated to the unconscious mind. Freud's work concerns the psychological role of dreams, which does not exclude any physiological role they may have. Sleep has an overall role of consolidation and organization of synaptic connections formed during the learning experience [26].

While penile erections are commonly believed to indicate dreams with sexual content, they are not more frequent during sexual dreams than they are during non-sexual dreams [27]. The parasympathetic nervous system experiences increased activity during REM sleep which may result in the erection of the penis or clitoris. In males, 80- 95% of erections a company's REM sleep while only about 12% of men's dreams contain sexual content [28]. Dreams are caused by random firing of neurons in the cerebral cortex during the REM period of sleep [29]. According to Hobson and McCarley (1977), in their activation synthesis theory,

the forebrain creates a story in an attempt to reconcile and make sense of the nonsensical sensory information presented to it.

Events transpiring during sleep and wakefulness are interwoven, each serving as antecedent and consequent condition [30]. The clock that influences the appearance of sleep and wakefulness may itself be reset by psychological processes [30]. Wakefulness can take on a multitude of casts, from normal renderings through aberrant forms and as night follows the day, so will sleep reflect this variation [30].

Cortical activity varies in association with behavior and sleep-wake states [31]. Cortical activity is predominantly fast during waking and paradoxical or REM sleep, and slow during quiet or Slow Wave Sleep [31]. The waking system, located in the reticular formation of the brain, is typically bombarded by cortical electrical stimulation [10]. In order for an individual to sleep this excitement of the waking system needs to be inhibited. (10).The fast cortical activity is reflective of cortical activation that is stimulated and maintained by sub cortical activating systems. These systems originate in the rostral brainstem where glutamatergic neurons of the reticular formation, cholinergic pontomesencephalic segmental neurons, and noradrenergic locus coeruleus neurons collectively comprise critical activating systems [32, 33]. They project forward through a dorsal pathway to the midline and intralaminar thalamic nuclei that form the nonspecific thalamo-cortical projection system. Excited by brainstem inputs, this thalamo-cortical system stimulates in turn widespread cortical activation [34].

Sleep inertia is the drowsiness, often associated with physical in coordination and occasionally with confusion that is present after waking from sleep [1]. It may be the effect of delayed activation of the prefrontal cortex at the transition from sleep to wakefulness [1]. If it is severe it may cause a confusional arousal in which lack of awareness is combined with often complex motor behavior. Sleep inertia often lasts 30-120 minutes after waking in the morning [1]. Sleep inertia almost always arises when waking occurs from NREM rather than REM, and in particularly NREM -3 (stage 3). It is most common after over sleeping, after day time naps if stage 3 NREM is entered, which is usual if naps last more than 30 minutes, and in idiopathic hypersomnia [1]. Sleep inertia can be shortened by caffeine, suggesting that it may be released to an increased influence of adenosine after the onset of wakefulness [1].

Aspects of REM sleep can also intrude into wakefulness. The ability recall dreams on awakening is a common example of this, and hallucinations associated with delirium, such delirium tremens, probably represent partial REM sleep intrusion into wakefulness [1]. The loss of muscle tone with laughter

(cataplexy) is an example of pathological REM sleep intrusion into wakefulness [1]. The intrusion of wakefulness into REM sleep is responsible for sleep paralysis at the end of the period of sleep [1].

Humans require different hours of sleep depending on age, new borns require 12-18 hours of sleep, Infants 14- 15 hours of sleep, Toddlers 12-14 hours of sleep, Preschoolers 11-13 hours of sleep, School age children 10-11 hours of sleep, Adolescents 8-9 hours of sleep, and adults 7-9 hours of sleep [1, 3, 35]. Whether an individual is awake or asleep depends on the balance of forces promoting and inhibiting each of the two states [36]. At times the balance can be almost equal and the subject may begin to fall asleep if he or she had previously been awake, or to lighten from sleep if previously asleep [3]. The mechanisms determining whether sleep or wakefulness predominates are not completely understood, but adaptive drive (light exposure, physical activity, social activity, food), ultradian sleep rhythms, and homeostatic sleep- wake mechanisms interact with each other and with circadian rhythms [3].

### Sleep Deprivation

Sleep deprivation is the condition that occurs when an individual fails to get enough sleep. This results in either extended periods of wakefulness or a decrease in sleep over an extended period of time. Sleep deprivation can either be chronic or acute. A chronic state of sleep deprivation can cause daytime sleepiness, clumsiness and weight loss or weight gain [37].

Investigators have performed three different types of sleep deprivation studies; Total Sleep Deprivation, Selective Sleep Stage Deprivation, and Partial Sleep Deprivation [8]. Total sleep deprivation of 150-200 hours has been associated with the development of brief psychotic episodes in some subjects, but apparently does not result in long-term psychological effects [8]. Selective stage sleep deprivation occurs if individuals are deprived of sleep during a sleep stage. If subjects are deprived of a sleep stage, an excessive amount of that stage will occur upon cessation of the deprivation. This concept is referred as the "rebound phenomenon" and may be seen following REM or NREM-3 (stage 3) [8]. Decreases in REM or NREM stage 3 can be produced whenever the polygraph indicates that the individual is entering that stage. REM sleep deprivation has been reported to impair memory of past events and acquisition of new data [8]. Partial sleep deprivation subjects are allowed restricted sleep time during several consecutive nights [8].

Sleep loss seems to activate the sympathetic nervous system, which can lead to a rise in blood pressure, and an increase in cortisol secretion [38, 39, 40]. The immune response may be impaired and metabolic changes such as insulin resistance may occur

[41]. People who are exposed to sleep loss usually experience a decline in cognitive performance and changes in mood [42]. Memory loss occurs when individuals do not sleep for long periods [43]. Attention to detail and vigilance, both linked to brain function, are also affected by the loss of sleep [43, 44, 45]. Sleep deprivation impairs visuomotor performance [46]. Sleep deprivation is also linked to the use of caffeine, alcohol, and nicotine [47]. Shift work also causes sleep deprivation [58].

It is clear from the ongoing research that sleep deprivation affects the nervous system, the immune system, the metabolic system, which can lead to weight gain/loss and diabetes, cognitive performance, mood, which can lead to irritability, lack of motivation, anxiety, symptoms of depression and social interactions. Memory loss, lack of attention, vigilance and vasomotor skills are also caused by sleep deprivation.

### Sleeplessness

Sleeplessness, also called insomnia, is a sleep disorder in which there is an inability to fall asleep or to stay asleep as long as desired [49, 50]. Sleeplessness is often thought of as both a symptom and a sign of a medical disorder [50, 51]. It can accompany several sleep, medical and psychiatric disorders characterized by a persistent difficulty falling asleep and/ or staying asleep or sleep of poor quality. Sleeplessness (insomnia) can be categorized as primary or secondary related to the disruption of circadian rhythm or to one of a number of special categories such as sleep apnea and sleep walking [52]. Secondary sleeplessness is caused by medical conditions, by psychological conditions and by problems associated with medications or drugs [52].

Sleeplessness is usually associated with emotional or mental tension, anxiety, depression, work problems, financial stress, unsatisfactory sex life and other partnered relationships. (9). Sleeplessness can also be associated with the use of, or even more frequently the attempt to withdraw from alcohol, nicotine or illicit drugs [52-54]. Chronic pain and noise can also cause individuals to develop sleeplessness [53, 54]. Changes in the level of steroid hormones, cortisol, estrogen, and progesterone cause sleeplessness [55, 56].

Sleeplessness can be treated by non-pharmacological means or medications. It is important to identify and rule out medical and psychological causes before deciding on a treatment for sleeplessness [57]. It is also important to identify and treat other medical conditions that may be contributing to sleeplessness such as depression, breathing problems and chronic pain [58].

The non-pharmacological treatment for sleeplessness include attention to sleep hygiene, stimulus control, behavioral interventions, sleep

restriction therapy, paradoxical intention, patient education, and relaxation therapy [59]. Behavioral therapy can assist an individual (patient) in developing different sleep behaviors to improve sleep quality and consolidation. Behavioral therapy includes learning healthy sleeping habits to promote sleep relaxation, undergoing light therapy to help with worry reduction strategies and regularize your biological clock [58]. Environmental modifications such as using the bed for sleep or sex only, not for activities such as reading or watching television, waking up at the same time every morning, including weekends; going to bed only when sleepy and when there is a high likelihood that sleep will occur, leaving the bed and beginning an activity in another location if sleep does not occur in a reasonably brief period of time after getting into bed, (~20 minutes), reducing the subjective effort and energy expended trying to fall asleep; avoiding exposure to bright light during nighttime hours, and eliminating daytime naps [60].

Medications such as antihistamines, benzodiazepines and non-benzodiazepines, antidepressants, melatonin, alcohol, and opioid medications are used in the treatment of sleeplessness [61-65].

### Sleep Medicine

Sleep Medicine is a branch of Medical Science developed to research and administer pharmacological and herbal medications in the treatment of sleep disorders such as sleep deprivation and sleeplessness. Early researchers extracted and identified sleep substances in the brain stems of sleep deprived rats [6]. This significant finding propelled research in the area of sleep medicine. The concept of humoral (body fluids) control of sleep was vigorously reviewed and rapidly established since the isolation and identification of delta sleep-inducing peptide [6]. It was found that uridine, uracil, and barbital all of which have a similar basic structure exhibited the same long lasting sleep – promoting effects as an isolated sleep promotary substance-B [6].

There are many sleep medications generally known as hypnotic sedatives that have been used in the treatment of sleeplessness (insomnia) [9]. The variety of drugs that are used suggests that a standard drug treatment for sleeplessness has not been established [9]. The drugs normally used to treat sleeplessness may be divided into two categories- barbiturates and non-barbiturates [9]. Additive barbiturates are amytal, seconal, Nembutal, and luminal. Among the non – barbiturates those presumably non-additive- are drugs called benzodiazepines such as Dalmane, Valium, Tranxene, Serax, Librium and Propanediol. Non-benzodiazepines such as Zolpidem, Zaleplon, Zopiclone, and Eszopiclone, in addition to some antidepressants such as Elavil, Sinequan, Amitriptyline, doxepin, Mirtazapine, and trazodone are also prescribed

to treat sleeplessness [10, 64, 62]. Some over the counter medications such as Benadryl and Nyquil are used as sleep aids.

Barbiturates are additive. Individuals who use such drugs have the tendency to want to increase their dosages as time passes [10]. This is a dangerous tendency because overdoses can be fatal [10]. One of the theories of the positive functions of barbiturates is that they will depress cortical activity-that is, they will depress the cortex that stimulates the reticular activating system or the wakeful system in the brain. When activity from the cortex is decreased, then the wakeful reticular activating system will become gradually deactivated and ultimately it will become inhibited. This inhibiting process permits the function of those systems in the brain that generate sleep and eventually with such inhibition, the troubled sleeper will sleep [10].

Non-barbiturate drugs may be divided into the broad categories, benzodiazepines, non-benzodiazepines, propanediols, and antidepressants. These non-barbiturates are presumably non-additive [10]. Benzodiazepines are the most widely prescribed class of hypnotic drugs for the treatment of sleeplessness. Benzodiazepines, while inducing unconsciousness, actually worsen sleep as they promote light sleep while decreasing time spent in deep sleep [66]. Benzodiazepines act by binding selectively to the GABA receptor [61, 67, 52]. There is generally little evidence for the benefit of benzodiazepines in the treatment of sleeplessness, or evidence of major harm and as a result prescription continues to increase [68].

Non-benzodiazepines are a class of sedative hypnotic medications used in the treatment of mild sleeplessness. The effectiveness of non-benzodiazepines at improving time to sleep is slight [64]. It is controversial whether non- benzodiazepines are superior to benzodiazepines. Some antidepressants are frequently quite effective in relieving sleeplessness [10]. Mirtazapine is known to decrease sleep latency, promoting sleep efficiency and increasing the total amount of sleeping time in individuals suffering from sleeplessness and depression [69]. It is known that the use of both benzodiazepines and antidepressants in the treatment of sleeplessness can lead to withdrawal effects, which can induce rebound sleeplessness.

Propanediols are used to promote sleep in tense patients. They can be toxic and side effects include slurred speech, physical and psychological dependence, and vertigo [10]. A sudden discontinuance of propanediols can cause sleeplessness, anorexia, and various withdrawal reactions such as tremors, vomiting, confusion, rash, headaches, and severe depression [10].

Sleeplessness is a common feature of Schizophrenia [70]. In order for sleeplessness to be

considered as a symptom related to schizophrenia, the sleep disturbance must last for at least one month and be associated with daytime fatigue or impaired daytime functioning [71]. Limited studies have shown that typical (haloperidol, thiothixene, flupentixol) and atypical antipsychotic drugs (olanzapine, clozapine, and risperidone) improve sleep induction and/or sleep maintenance in schizophrenia patients [70].

Antipsychotic drugs use a variety of mechanisms to induce sleep. Typical and atypical antipsychotic drugs bind to a wide variety of Central Nervous System (CNS) receptors [70]. They produce effects by blocking dopamine, serotonin,  $\alpha$ -adrenergic, histamine, and acetylcholine (muscarinic) receptors. Irrespective of their chemical structure antipsychotics show intermediate, (clozapine) to high (haloperidol, flupentixol, thiothixene, olanzapine, risperidone) affinity for the D2 receptor of dopamine [70]. Additionally, clozapine and olanzapine have intermediate affinity for the D1, receptor of dopamine. (70). In contrast to the classical antipsychotics, the newer antipsychotics show high affinity for the serotonin (5-HT<sub>2A</sub>) receptor and to a lesser extent for the serotonin (5HT<sub>2c</sub>, 5HT<sub>6</sub>), clozapine, olanzapine, and the serotonin (5HT<sub>7</sub>), risperidone receptor. Olanzapine, risperidone, and clozapine bind with high affinity to the  $\alpha$ 1 adrenoceptor, whereas olanzapine and clozapine display high affinity for both histamine and acetylcholine receptor [72- 75].

The blockage of the dopamine (D2) receptors has been proposed to be responsible for the improvement of positive symptoms [70]. Moreover, the blockage of serotonin (5-HT<sub>2A</sub>) receptors contributes to the improvement of negative symptoms and cognitive functions. On the other hand the blockage of  $\alpha$ -adrenergic ( $\alpha$ 1), histamine (H1) and acetylcholine receptors induce a number of side effects [70]. The blockage of the dopamine (D2) receptors. The blockage of the dopamine (D2) receptors could be partly responsible for the improvement of sleep in schizophrenic patients [70]. However, the amelioration of sleep has been related almost exclusively to the blockage of  $\alpha$ -adrenergic ( $\alpha$ 1), histamine (H1), and acetylcholine (muscarinic) receptors [70]. This is based on the premise that  $\alpha$ -adrenergic ( $\alpha$ 1) (pyrilamine, diphenhydramine) or acetylcholine (muscarinic) receptor (scopolamine) antagonists produce somnolence, and increase likelihood of falling asleep and reduced concentration [76-78]. It has been demonstrated that the serotonin (5HT<sub>2a/c</sub>) receptor antagonist ritanserin selectively increase slow wave sleep in normal volunteers [79, 80]. A similar effect has been described for patients suffering with sleeplessness [81, 82].

Alcohol is often used as a form of self-treatment of sleeplessness to induce sleep. Long term use of alcohol is associated with a decrease in NREM

stage 3 sleep as well as suppression of REM sleep and REM sleep fragmentation. Frequent moving between sleep stages occurs with awakenings due to headaches, the need to urinate, hydration, and excessive sweating. Glutamine rebound also plays a role when someone is drinking. Alcohol inhibits the amino acid glutamine, which is one of the body's natural stimulants. When the person stops drinking, the body tries to make up for lost time by producing more glutamine than is needed. The increase in glutamine levels stimulates the brain while the drinker is trying to sleep, keeping him/her from reaching the deepest levels of sleep [83]. Eliminating chronic alcohol use can lead to severe sleeplessness with vivid dreams, and during withdrawal REM sleep is typically exaggerated as part of a rebound effect [84].

Herbal medicines have been shown to induce sleep in individuals suffering from sleeplessness [85]. To date, the most widely studied herbs are valerian, (*Valeriana officinalis*), Kava (*Piper methysticum*), Passion flower, (family Passifloraceae), Chamomile- (which refers to two similar species of plants: the German Chamomile (*Matricaria recutita*, and the Roman Chamomile (*Chamaemelum nobile*), both of which are members of the Asteraceae family. Other not so well studied sedative herbs are Catnip, (*Nepeta cataria*), Hops (*Humulus lupulus*), Skullcap, (*Scutellaria laterifolia*), Lemon Balm, (*Melissa officinalis*) and St. John's Wort (*Hypericum perforatum*).

Valerian (*Valeriana officinalis*) is a native to Europe and Asia, but now grows in most parts of the world [86]. Valerian's primary chemical constituents are monoterpenes, sesquiterpenes, and alkaloids [85]. The monoterpenes include 1-borneol, valenol, valeranone, and valmane [85]. A subgroup of the monoterpenes is valepotriates, which include valtrate and its derivatives, baldrinal and homobaldrinal [87]. However, valepotriates rapidly decomposed in the stored herb, so their content in valerian preparations is low [88]. The sesquiterpenes present in valerian include isovaleric acid, valeronic acid, valernal, valeranone, and valerenol [85]. The alkaloids found in valerian include valeranine and actinide. *Valeriana officinalis* has a relatively high content of sesquiterpenes and a low content of valoptriates [85].

The mechanisms of action of valerian are not entirely understood, but they likely involve facilitation of GABA transmission [85]. Low micrograms concentrations of an aqueous extract of valerian inhibits uptake and stimulates the release of GABA from synaptosomes [89, 90]. Valeronic acid also inhibits breakdown of GABA [85]. Low concentrations of valerian extracts enhance benzodiazepine binding [91]. A flavanoid, 6-methylapigenin, has been isolated from *Valeriana wallichii* that may confer a benzodiazepine mechanism to this species [92]. The valoptriates may have central depressant effects through in vivo conversion to homobaldrinal [93]. Valerian extracts

show sedative effects in animals that are a dose dependent manner [94, 95]. Valerian improves subjective ratings of sleep particularly when taken nightly over one to two week periods [96]. No health hazards have yet been reported with the normal use of valerian, and it has been approved by the German Commission E as a treatment for anxiety and sleep [96].

Kava (*Piper methysticum*) is a plant native to the South Pacific islands [97]. The pharmacologically active chemicals found in kava are collectively known as kavalactones [85]. Kava facilitates GABA transmission. Low micromolar concentrations of kava extracts enhance the binding of ligands to the GABA receptor, potentiating binding of GABA and enhancing chloride ion influx [98, 99]. Kavalactones do not alter the binding of flunitrazepam, so their effect on GABA is not through the benzodiazepine receptor [100]. Despite its potential for improving sleep, only two studies have formally investigated it. One study found that six week daily treatment with kava reduced stress-induced sleeplessness [101]. The other study found that kava extract can improve anxiety related sleep problems, ameliorating quality and restorative aspects of sleep [102]. Kava has been approved by the German Commission E for the treatment of anxiety and sleeplessness [85].

A few members of the passionflower family (*Passifloraceae*) have sedative and anxiolytic effects [85]. The genus most studied is *Passiflora incarnata*. The whole plant or aerial parts are used for medicinal effects [85]. The most studied constituent of passionflower is chrysin. Chrysin binds to benzodiazepine receptors with micromolar affinity and competes for binding with the benzodiazepine, flunitrazepam [103]. Anxiolytic effects of chrysin are blocked by flumazenil, arguing for a benzodiazepine mechanism [104]. However, chrysin antagonized the electrophysiological effects of GABA at GABA<sub>A</sub> receptors [105]. These conflicting affects need to be reconciled with further, more careful research, although a partial benzodiazepine agonist mechanism is still possible and other mechanisms may exist [85]. A small controlled trial showed that passionflower extract improved anxiety in general anxiety disorder better than placebo [106]. There are no formal studies on the toxicity of passionflower and no adverse effects have been reported [85].

Chamomile refers to two similar species of plants: German Chamomile and the Roman chamomile, both of which are members of the *Asteraceae* family [85]. Chamomile has been used throughout the Egyptian, Roman and Greek cultures; is a native plant to Europe, Africa, and Asia and is naturalized to North America [85]. The flower tops are often dried and used in the form of a tea. Chamomile contains terpenoids as well as the flavanoids, apigenin, and apigenin-7-glucoside [107]. Apigenin is the most

studied compound in Chamomile. Apigenin binds with micromolar affinity at benzodiazepine receptors, or the GABA binding site of the GABA<sub>A</sub> channel [108]. However, other researchers found an antagonistic affect at GABA channels, which are insensitive to flumazenil [105]. While another study confirmed a sedative effect of apigenin in mice, it failed to reverse the effect with flumazenil [104].

Apigenin showed anxiolytic effects in mice, but no anti-seizure effects [108]. At doses ten times than required for anxiolytic effects, apigenin showed mild sedative effects [85]. Because doubt has been cast on a benzodiazepine mechanism for apigenin, other mechanisms by apigenin, including flavonoids must be evaluated [85]. Controlled trials of chamomile preparations must be carried out on humans [85]. Chamomile appears very low in toxicity and it has been listed as Generally Regarded as Safe (GRAS) by the Food and Drug Administration [85].

Other sedative herbs such as catnip, hops, skullcap, lemon balm, and St. John's Wort, have far less empirical research to support their use in improving aspects of sleep. However, there is research for each suggesting that further research is warranted. Catnip has a long recorded history of use and is noted for sedative properties in humans [85]. One reported accidental ingestion by a young child reportedly produced sedative effects [109]. Hops (*Humulus lupulus*) is reputed to produce anxiolytic and sedative effects. The active agent is thought to be 2-methyl-3-butene-2-ol, since it produces sedation when injected intraperitoneally in mice [110]. Skullcap (*Scutellaria laterifolia*) is an herb that has been used in Chinese and Western medicine for sedative and antiseizure effects [111]. Skullcap contains the flavanoids baicalin and baicalein, and the amino acid glutamine, so GABAergic mechanisms are possible [112]. Lemon balm (*Melissa officinalis*) has shown sedative effects and analgesic activity in mice [113]. It also increases the sedative activity of a barbiturate (pentobarbital). A controlled study in humans demonstrated binding of lemon balm constituents to muscarinic and nicotinic receptors in human cerebral cortex tissue [114]. St. John's Wort (*Hypericum perforatum*) has potential for the treatment of sleep disorders. Controlled studies of St. John's Wort show that it increases slow wave sleep and increases REM latency [115, 116]. Active constituents have been identified in St. John's Wort which have a variety of mechanisms (blocking reuptake, weak inhibition of MAO and COMT), as well as effects on adenosine, GABA, and Glutamate receptors [117]. Chronic use of St. John's Wort leads to adaptation of monoamine receptors and serious side effects from St. John's Wort monotherapy have not yet been reported [85].



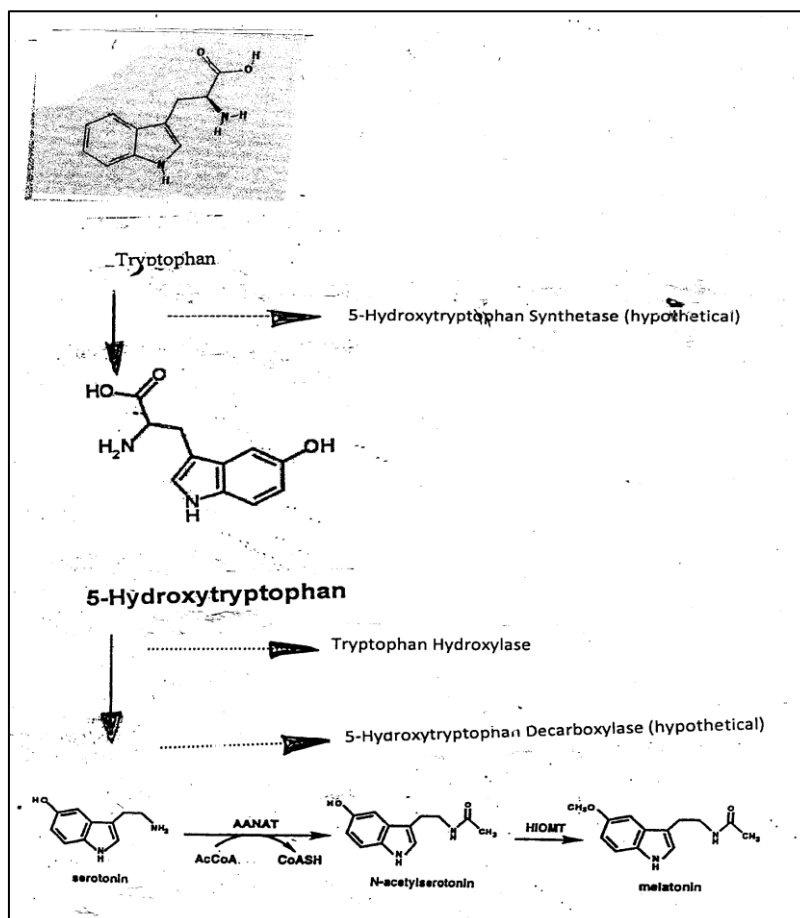
## Biochemistry of Sleep

Like all other processes in living organisms sleep is controlled by biochemical reactions. Several hormones and enzymes are involved in the processes that produce sleepiness and wakefulness. Adenosine a byproduct of energy consumption in the body is thought to accumulate in the body throughout the day, generating a feeling of tiredness and sleepiness, which marks the beginning of the sleep process and then remove when we sleep. The most important chemical which regulates the sleep wake process is the hormone melatonin.

Melatonin is a hormone found in all living creatures. It is produced by the pineal gland in the brain. Circulating levels of melatonin are always high at night and low during the day reflecting rhythmic changes in the synthesis of melatonin by the pineal gland [118]. The large increase in the production of melatonin at night is due to a concomitant increase in the penultimate enzyme in melatonin synthesis Arylalkylamine-N-acetyltransferase (Serotonin N acetyltransferase) AANAT [118]. Melatonin is synthesized from the amino acid tryptophan (Figure 1). Tryptophan cannot be synthesized by humans and must be obtained in the diet. The activity of two enzymes in

the pathway, Tryptophan hydroxylase (TPH) and Arylalkylamine N acetyltransferase (AANAT), display circadian rhythms [7]. The production of melatonin in the pineal gland is thought to be regulated by two mechanisms. One mechanism is clock-driven changes in TPH and AANAT mRNAs, which in turn drive changes in the synthesis of the corresponding encoded proteins. The other mechanism is light induced post-transcriptional degradation of AANAT. These two mechanisms insure that melatonin production follows a precise schedule that reflects daily changes in environmental lighting [7].

The major biomolecules that are involved in the production of normal sleep, the neurotransmitter serotonin and the hormone melatonin are both synthesized from tryptophan (Figure 1). Tryptophan has been shown to increase sleep time in some studies, while others show no effect on the parameter [10]. Although the synthesis of serotonin accounts for only a small amount of the total tryptophan used by the body, it is the major metabolic route found in the brain [10]. Five hydroxytryptophan (5-HTP), the immediate precursor of serotonin (Figure 1) has been administered orally and intravenously to human subjects and have produced either no changes or increases in REM sleep.



**Figure 1: Showing the Synthesis of Melatonin from Tryptophan and two Hypothetical Enzymes that might also be involved in the Process (Modified after Hickman *et al.*, 1999)**

**According to Mendelson and his Colleagues (1977):**

1. Human studies involving serotonin precursors and synthesis inhibitors suggest that. Within limits, serotonin concentrations are directly correlated with the amounts of REM sleep. Rapid decreases in serotonin, induced by high doses of Parachlorophenyl-alanine (PCPA), an inhibitor of the enzyme Tryptophan hydroxylase, in animals or discontinuation of 5-hydroxytryptophan or phenelzine in man, may result in a syndrome of sleeplessness and hyperactivity. One hypothesis that seems to account for a great deal of data is that serotonergic systems are involved in confining phase events to REM sleep.
2. In contrast to serotonin, it appears likely that levels of norepinephrine are inversely related to the amounts of REM sleep. Drugs blocking dopaminergic receptors appear to have relatively little effect on sleep in normal humans [10]. The body seems to be able to adapt to pharmacologic manipulation of serotonin and norepinephrine, and to go through withdrawal period of readjustment when modifying drugs are discontinued [10].
3. A cholinesterase inhibitor, which increases cholinergic activity, can induce periods of REM sleep. It appears likely that cholinergic mechanisms are involved in the initiation of REM sleep and waking episodes. A precursor of histamine seems to have little effect on the sleep of normal narcoleptic humans.
4. It seems likely that other neurotransmitters other than serotonin, norepinephrine, and acetylcholine may play a role in the regulation of sleep.

The amino acid, Glycine, has been reported to improve the quality of sleep [119]. Bennai and Kawai (2012) reported that the non-essential amino acid glycine has indispensable role in both excitatory and inhibitory neurotransmission via N-methyl-D-aspartate type glutamate receptors and glycine receptors respectively. They found that glycine decreases core body temperature and suggested that core body temperature might be the mechanism underlying glycine's effect on sleep. The onset of sleep is known to involve a reduction in the core body temperature.

Other chemical substances used by individuals or sometimes administered by medical professionals have a biochemical effect on sleep but further research is needed to determine their mode of action. Amphetamines are used to treat narcolepsy. Their most common effects are anxiety, sleeplessness, stimulation, increased alertness, and decreased hunger. The administration of amphetamines has been reported to cause a decrease in the percentage of REM sleep [10]. Caffeine is a stimulant that works by slowing the action of the hormones in the brain that cause somnolence, particularly by acting as an antagonist at adenosine receptors. The effective dosage of caffeine is individual, and in part depends on prior usage. It can cause a rapid

reduction in alertness as it wears off. Cocaine and crack cocaine have an effect on sleep. Studies on cocaine have shown its effects to be mediated through the circadian rhythm system [120]. This may be related to the onset of oversleeping in regard to cocaine induced sleep disorder [120]. A class of drugs known as emohathogen- entacogens, keep users awake with intense euphoria, commonly known as ecstasy. Methylphenidate has a similar effect on users with actions similar to amphetamines and cocaine, and its chemical composition resembles that of cocaine. Tobacco has been shown that users describe more daytime drowsiness than non-smokers. Other analeptic drugs such as Modafinal and Armodafinal are prescribed to treat narcolepsy, idiopathic hyperomnia, shift work disorder, and other conditions causing excessive daytime sleepiness. The precise mechanism of analeptic drugs on the CNS is unknown, but they have been shown to increase both the release of monoamine and levels of hypothalamic histamine, thereby promoting wakefulness. Some individuals use marijuana to induce sleepiness. Users often report relaxation and drowsiness. It has been shown that Tetrahydrocannabinol, the principal psychoactive constituent in marijuana, reduces the amount of REM sleep [121]. Frequent users of marijuana often report being unable to recall dreams. A large meal can make an individual feel sleepy. This post lunch dip is mostly an effect of the biological clock, and as a result individuals tend to feel very sleepy two times a day, twelve hours apart.

**Sleep and Society**

Sleep is increasingly being recognized as important to public health. In recognition to the importance of sleep to the nation's health, the Institute of Medicine encourage collaboration between the Center for Disease Control and the National Center on Sleep Disorder Research to support the development and expansion of adequate surveillance of the USA population's sleep pattern and associated outcomes. Two recent reports on the prevalence of unhealthy sleep behaviors and self-reported sleep related difficulties among USA adults provide further evidence that insufficient sleep is important to public health.

Sleep deprivation is a common place occurrence in modern culture. Every day there seems to be twice as much work and half as much time to complete it in. The results in either extended periods of wakefulness or the decrease in sleep over an extended period of time. While some individuals may like to believe that they can train their bodies not to require as much sleep as they once did this belief is false [122].

Research suggests that sleep patterns vary across cultures [123]. Sleep in adults is usually taken as a single episode at night (monphasic pattern, but in 85% of mammals, especially those with a small body mass, sleep is polyphasic [1]. A single prolonged sleep

episode these animals to more danger [1]. A monophasic pattern enables the sleep debt accumulated during the waking period to be fully discharged whereas a polyphasic routine pays back this a sleep debt in smaller units [1].

In many nomadic or hunter gatherer societies, people will sleep on and off throughout the day or night depending on what is happening [12, 30]. There is evidence that hunter –gatherer societies adopt a polyphasic sleep pattern with at any one time 25% of the population awake at night and 10% sleeping during the day [1]. A concern with this sleep pattern is that there are repetitive episodes of sleep inertia if naps last more than 20 minutes, and particularly if they are longer than 60 minutes [1]. This polyphasic pattern in hunter-gather communities, however, reduces exposure to danger, and enables a broader division of labor in the society [1].

Although a monophasic pattern is usual in adults, children obtain polyphasic sleep, usually around 3-5 hours during the day at the age of 6 months and 2 hours during the day at 2 years [1]. Initially, these sleep episodes are mainly random, but once the circadian rhythms mature at 3-6 months, more sleep is obtained at night than during the day. The polyphasic pattern is often re-entered in the elderly who tend to nap during the day time, but occasionally it is retained throughout life [1]. A polyphasic sleep pattern lessens the performance loss during sleep deprivation. The frequent naps repay the sleep debt exponential [1]. The deeper NREM sleep at the start of each nap is more time effective than a more prolonged sleep episode with relatively lighter NREM and REM sleep [1]. Repayment of the sleep debt is well facilitated if naps are coincided with an increased circadian or adaptive drive to fall asleep.

A biphasic sleep pattern is often adopted in the Mediterranean countries, with a siesta taken in the mid-afternoon, and it is common for nocturnal sleep to be postponed until after mid-night [1]. This pattern reflects the circadian tendency to promote sleep during the afternoon and at night, but in addition to this biological element there is probably a cultural factor [1]. The siesta avoids taking physical activity during the hottest part of the day [1]. The influence of the REM sleep ultradian 90-minute cycle on the timing of sleep is uncertain. A 90-minute cycling in reaction time performance and the tendency to daydream has been found, but it is uncertain whether or not this predisposes to enter sleep at these times> [1]. Most people have a tendency to be more alert early in the morning soon after waking (morning types) or late at night prior to falling to sleep (evening types). There is a tendency during adolescence to become an evening type and from early adult life on wards to progressively become a morning type by old age [1].

Plentiful artificial light has been available in the industrial west since at least the mid-19<sup>th</sup> century, and sleep patterns have change significantly everywhere that lighting has been introduced [123]. In general people sleep in a more concentrated burst through the night, going to sleep much later, although this is not always true [123]. Historian, Roger Ekrick, thinks that the traditional pattern of segmented sleep as it is sometimes called began to disappear among the urban upper class of Europe in the late 17<sup>th</sup> century and the change spread over the next 200 years and by the 1920s the idea of a first and second sleep had receded entirely from our social consciousness [124]. Ekrick attributed the change to increases in street lightning, domestic lighting, and a surge in coffee houses, which slowly made night time a legitimate time for activity, decreasing the time available for rest [124].

People generally sleep with at least one other person (sometimes many) or with animals. In almost all societies, sleeping partners are strongly regulated by social standards [123]. For example, people might only sleep with their immediate family, extended family, spouses, peers of equal social rank, or with no one at all [123]. Sleep may be an active social time, depending on the sleep groupings, with no constraints on noise or activity [123].

People sleep in a variety of locations. Some sleep directly on the ground; others on skin or blanket; others sleep on platforms or beds. Some sleep with blankets, some with pillows, some with simple headrest; some with no head support [123]. These choices are shaped by a variety of factors, such as climate, protection from predators, housing type, technology, personal preference, and the incidence of pests [123].

Insufficient sleep may be caused by shift work, extensive travel time (jet lag), around the clock access to technology, work schedules, and increased social activity at night [123]. In addition to the chronic self-inflicted health problems such as heart disease, kidney disease, hypertension, diabetes, stroke, obesity, depression and sleeplessness, there is a cost to society of increased medical bills and long-term care. There is also an increased in mortality and reduced quality of life. In the work place insufficient sleep can lead to a reduction in memory, alertness, loss of productivity, and increased in accidents. Sleep deficiency is also associated with an increased risk of injuries in adults, teens and children. Driver sleepiness (not related to alcohol) is responsible for serious car crash and injuries and death. The American Academy of Sleep Medicine (AASM) reports that one in every five serious motor vehicle injuries is related to driver fatigue; with 80,000 drivers falling asleep behind the wheel and 250,000 accidents every year related sleep [125]. The National Highway Traffic Safety Administration suggested that the figure for traffic accidents may be closure to

100.000 [126]. The AASM recommends that individuals should pull off the road and take a 15-20 minute nap to alleviate drowsiness [125]. In the elderly sleep deficiency might be linked to an increased risk of falls and broken bones.

The promotion of good sleep habits and sleep is known as sleep as hygiene. The following sleep hygiene tips can be used to improve sleep and reduce the chance that you may be a burden to society.

1. Go to be at the same time each night rise at the same time each morning. This is not possible if you work nights, but you have specific sleep and wake times during the day.
2. Avoid large meals before bedtime.
3. Avoid caffeine and alcohol close to bed time.
4. Avoid alcohol and other stimulants.

## CONCLUSION

Sleep is a fundamental process to living organisms. In humans sleep deprivation leads to many complications, physical, mental and medical. The discovery of REM and NREM sleep were important to our understanding of the sleep/wake process. The importance of the importance of dreaming to sleep needs further research. The electrocephalogram played an important role in our understanding of the sleep process. Pieron's initial idea propelled modern sleep research [127]. Jouvet's writings on paradoxical sleep helped to explain the sleep/wake process [128].

Sleeplessness, an inability to fall asleep is both a symptom and a sign of a medical disorder. It can also be a psychiatric disorder. To treat sleeplessness, the cause of the problem must be established. Once the problem has been determined a treatment schedule can be followed.

Sleep Medicine is in its early stages of development. The numerous different types of drugs administered to treat sleep disorders would suggest that no "wonder" drug has been discovered. A look at herbal medication seems to be an obvious course of action. The limited research on medicinal plant extracts seems promising. I suggest that we use extracts rather than try to determine the most active ingredient, since it is possible that other components would play a role in alleviating side effects.

A biochemical approach to sleep would enable research to determine which hormones, enzymes and other biomolecules other than melatonin and serotonin that are involved in the sleep process. From Figure 1, it is possible that such enzymes as a 5-hydroxytryptophan synthetase and 5-hydroxytryptophan decarboxylase might be involved in the process. It is possible that other neurotransmitters than serotonin, norepinephrine or acetylcholine are involved in the sleep process. The amino acid tryptophan plays an important role in sleep

biochemistry but the role of glycine needs further research. Stimulants and other drugs such as marijuana needs further research to determine their importance.

The role of sleep in society has become an important phenomenon only as it relates to sleep deprivation and its effect. The main problems of insufficient sleep to a society are increased medical costs to its members and government, loss of productivity at work, human error causing work related accidents, and automobile accidents due to driver fatigue.

Due to behavioral changes in the society, such as shift work, increased worked hours and extensive socialization, it is possible for adult sleep patterns to become polyphasic with regular naps to repay the sleep debt.

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