1:46 a.m. Do any of these scenes sound familiar to you?

- The bright light from your phone welts your eyes and keeps you up until just hours before you have to go to class.
- Sitting under the heavy fluorescent lights of the library, your textbook looks up at your heavy eyes which are starting to become reigneited by a second wave of awareness.
- Dim rays from your desk lamp keep your table under a glow, since the sun has long since disappeared.

Your melatonin most likely has been affected in all of these situations. Read on to find out how and why melatonin takes part in any of these situations.

**What Is Melatonin?**

Melatonin, as heard of by most, is controlled by your natural sleep and wake cycles where light can be a primary factor in the unnatural effect of the body’s production of melatonin. Usually, the body raises its production of endogenous melatonin in the evening. The level of melatonin will stay raised throughout the night, and will begin to decrease in the early morning, when the levels of melatonin in the body are nearly undetectable. Naturally, this cycle lasts around 8 hours during the night and 16 hours during the daytime [1]. However, light can make the body produce melatonin either later or earlier than when it is normally produced [2]. When there is more hours of daylight in the summer, the production of melatonin becomes shorter, and longer with the fewer number of winter daylight hours.

Melatonin production starts with the amino acid tryptophan and the intermediary serotonin. Then, it is released to areas of the body that control the sleep and wake cycles such as the brain and eyes. When this endogenous hormone cannot be produced, however, many people turn to the exogenous hormone to take in order to assist themselves into a more naturally
functioning circadian rhythm. Melatonin supplements are made synthetically and can be purchased without a prescription [1].

History of Melatonin and Its Discovery

The exploration of melatonin has begun only fairly recently when in 1958, Aaron Lerner discovered it in mammals, and in 1981 when Alfred Lewy uncovered that bright light had an effect on it [3]. In 1958, when Lerner successfully isolated melatonin from pineal extracts, he found that it lightened the skin color of fish, tadpoles, frogs, and toads, leading him to think it would be useful in dermatology [4]. Aaron Lerner and his colleagues incorrectly identified the hormone to be an effective treatment for vitiligo, and even tried to use it as a treatment for other dermatological uses. It was only until later that it was discovered that melatonin took its effect on the brain [5].

Although the research on melatonin has been fairly recent, the discovery of the gland it comes from is not. There is documented discussion on the pineal all the way back from 130 to 200 A.D., most likely though to come from Galen. Galen did not discover the gland, however he was the first to have written about its location, structure, form, and function. Because the workings of the gland were so unknown, actually studies of its workings did not start to be studied until the 1950s [4].

Where is Melatonin Anatomically Found and Produced and How it Works

Endogenous melatonin is produced in the pineal gland in the brain as a lipid soluble molecule. As mentioned before, it is synthesized from the amino acid tryptophan, then crosses blood-brain barrier, being released into the blood and cerebrospinal fluid. It is in the blood-brain barrier that the lipid solubility of melatonin becomes significant. In the brain and other parts of the body, it sends signals to the melatonin receptor, allowing the sleep and wake cycle to occur [1]. This is the direct link between sleep and melatonin, and why an increase in melatonin helps you sleep. Yet although it is known that melatonin helps sleep, it is relatively obscure how the process actually happens since there is no simple genetic model. However, in a study with zebrafish, whose sleep qualities were found to be similar those of sleep in mammals, it was found that a sleep-like state was induced through melatonin specific membrane receptors [6]. Thus, it is probable that this function is the same in humans. Exogenous melatonin is similar in that it mimics the effects of endogenous melatonin. However, it does not work for everyone, especially for all sleep disorders [7].

The Effect of Light

Light at night disrupts normal sleep patterns because it blocks the production of melatonin. A research study from the US National Library of medicine stated that “light [is] the most dominant synchronizer of melatonin production” [8]. It was published in the study that
phase shifts of producing more melatonin (of night-day sleep and wake cycles) could be facilitated by not using or reducing the amount of light exposure one has. In the study, people who needed help with advancing their phase shift at night wore orange glasses that blocked blue light from coming through, which the circadian rhythm is most sensitive to, were able to enter the phase shift in advance compared to if they were subjected to the blue light. Additionally, the study showed that participants in the study who wore the blue blocker glasses while also being in a room where the lights were dimmed, were able to enter the sleep phase shift one hour before those who were subjected to maximum light exposure with the glasses.

This suggests that the blue light emitted from often used cell phones or tablets right before going to bed may be part of the problem for not being able to fall asleep as fast as someone normally would who does not use their phone at night. It was suggested in the study that dimming the screens and wearing blue blocker glasses may be helpful in reducing the amount of blue light that enters the eyes, and therefore would help the chances of earlier melatonin production for sleep.

Melatonin in Plants
Melatonin was first discovered outside of animals in the 1960’s where it was found in coffee extracts and thought to be a byproduct of the extraction process. Since then it has been found in every plant that has been studied since and in every part of the plant such as leaves, stems, roots, fruits, and seeds. The amount of melatonin differs between plant species, plant part, and individual organisms based on their growing conditions. According to a phytomelatonin review, experimental evidence points toward melatonin being used as an antioxidant or growth promoter in plants. However, it has also been suggested that melatonin is useful in seasonal responses, regulation of plant reproductive cycles, its participation as a free radical scavenging agent, increase in the production of protective enzymes, and defense of plant cells against apoptosis (programmed cell death) caused by a harsh environment [20]. These environmental triggers include biological stresses such as a fungal infection, as well as nonbiological stresses such as temperature extremes, soil composition, drought, and toxins. Because plants are stationary and are not able to escape from environmental stressors, they contain a much higher level of melatonin than animals.

This is notable because humans ingest these plants in the form of common foods and beverages such as coffee, tea, beer, corn, rice, and wheat, to name a few. When birds ingest food with high melatonin levels, the melatonin binds to the melatonin receptors in their brains. In contrast, when humans ingest melatonin-rich food, the blood levels of melatonin increase significantly. Additionally, researchers have noticed that those in Mediterranean populations have a lower incidence of chronic-degenerative disorders. This has been attributed to their diets and how rich it is in certain phytochemicals (biologically active chemicals in plants), with melatonin being among them. It has been seen to lower the risk of cancer, cardiovascular disease, and diseases that degrade the brain; however, the experiments are fairly new and incomplete.

Melatonin Side Effects
Melatonin is a mostly safe supplement when taken by mouth over a three-month basis in low doses. In a Canadian scientific review that searched metadata of double blind experiments, it was found that the reported side effects of headaches, dizziness, nausea, and daytime sleepiness
were reported in placebos at the same rate that they were reported with melatonin [17]. However, Mayoclinic still warns that these are the most common side effects. Other, less common, side effects may include abdominal cramps, mild tremor, confusion or disorientation, reduced alertness, mild anxiety, and hypotension [15]. Additionally, melatonin may also cause drowsiness during the day, which makes driving or operating machinery ill-advised if one has taken a supplement in the past five hours.

Another concern is that exogenous melatonin may interact with medications such as anticoagulants (medicines that stop your blood from clotting), anti-platelet drugs, anticonvulsants, contraceptives, diabetes medications, and immunosuppressants [15]. There is conflicting literature over if melatonin supplements act as moderators of the immune system and relieve or worsen symptoms of autoimmune disorders. According to the American Cancer Society, if melatonin does in fact increase the strength of the immune system, this can actually worsen symptoms of severe allergies, lymphoma, rheumatoid arthritis, and other conditions that are caused by overactive immune systems [19]. In regard to anticoagulants, a University of Maryland Medical Center paper revealed that, “melatonin may increase the risk of bleeding from anticoagulant medications such as warfarin” [21]. If melatonin slows blood clotting, taking melatonin may lead to excessive bruising or bleeding. Melatonin may also produce this side effect if taken with herbs that slow blood clotting. This includes common herbs such as garlic and ginger [19]. The effects of melatonin on the reproductive cycle are not known, however the chemical was tried as a contraceptive in the 1990s [18]. Contemporary birth control increases melatonin levels in the body. Melatonin should be avoided in pregnancy, during breastfeeding or when trying to conceive. Additionally, children or adolescents should not use melatonin supplements as melatonin may interact with other hormones and interfere with their development.

Melatonin may react with other drugs or treatments and result in elevated melatonin levels. Using melatonin at the same time as sedatives may cause excessive sleepiness. Additionally, fluvoxamine can increase the amount of melatonin absorbed in the body, enhancing all the effects, negative and positive of supplements. Similar effects are seen with herbs such as catnip and St. John’s wort [19].

**Other Causes of Irregular Melatonin Production**

Several other disruptions to the production of melatonin exist in addition to the existence of light. A natural problem associated with the abnormal cycle of the production of melatonin is the aging process. This is evidenced by insomnia and early wakening, which is seen often in adults. In these cases, melatonin is suspected to be able to assist in adjusting the sleep and wake hours of these individuals. In a study published by the Agency for Healthcare Research and quality, it was shown that melatonin supplements moved up the time it took people with a primary sleeping disorder to fall asleep by an average of 10.7 minutes [16]. However, it was shown that the supplement was more effective in people who had delayed sleep phase syndrome rather than insomnia, however where “individuals with delayed sleep phase syndrome are distinguished from individuals with insomnia by the presence of a circadian abnormality”. But since it was concluded that melatonin was more effective as a sleep phase re-setter rather than a hypnotic, it could still be useful in individuals with insomnia and early wakening by adjusting their sleep rhythm cycle.
Chemical Properties of Melatonin

The chemical formula of melatonin is C₁₃H₁₆N₂O₂. It is most often seen as an “off-white powder.” Melatonin has a molar mass of 232.28 g/mol and a density of 1.175 g/cm³. Melatonin’s melting point is typically between 116.5°C and 118°C. Additionally, the boiling point is 512.8°C [26]. Melatonin is at 700 mV in the electrochemical series [27]. It is also known to be lipid-soluble [29]. Interestingly, melatonin is typically more heavily concentrated in flowers and seeds than it is in human blood [28]. Melatonin has many more additional, interesting chemical properties and processes, such as how it is synthesized in the human body.

Chemical Reactions in the Biological Synthesis of Melatonin

Another important aspect of melatonin is the chemical process in which it is biologically synthesized. The natural production of melatonin is inhibited by light. That being said, the absence of light signals the brain to begin the production of melatonin. There are several chemical reactions that must take place to synthesize melatonin [24]. The following reactions take place in the synthesis of melatonin in the pineal gland of humans; although, research has suggested that melatonin can also be produced in skin and hair [25]. Tryptophan, an amino acid, is the chemical that starts the process. Tryptophan hydroxylase is an enzyme that acts as a catalyst in a reaction that converts tryptophan into 5-hydroxytryptophan. Aromatic amino acid decarboxylase then acts as a catalyst to convert the 5-hydroxytryptophan into serotonin. The enzyme serotonin-N-acetyltransferase, also known as SNAT, allows for the conversion of serotonin into N-acetylserotonin [24]. It is useful to note that the amount of melatonin produced is dependent on the amount of SNAT available [27]. Finally, N-acetylserotonin is converted into melatonin with the help of the enzyme hydroxyindole-O-methyltransferase, or HIOMT [24]. At this point the synthesis is complete and the melatonin is free to perform its necessary functions.

This diagram provides a visual representation of the chemical reactions that take place during the production of melatonin in the human pineal gland [24].
The melatonin produced then proceeds to the cerebrospinal fluid and the blood stream. Once in the bloodstream, it binds to albumin, so that it can easily be carried throughout the entire body. Melatonin will later be broken down primarily by the liver, but the kidneys will break down a small amount [29]. Some melatonin will then be released in urine. There are other various potential methods for the breakdown of melatonin [25].

**Antioxidant Characteristics of Melatonin**

Although melatonin is most known for its connection to sleep, many studies have demonstrated the presence of antioxidant properties in melatonin. Melatonin is effective in counteracting damage from one small cell to the entire organism [28]. Interestingly, it has been shown to counteract the effects of oxidative damage in several health conditions and diseases. These antioxidant properties primarily occur in the electron transfer process. Melatonin’s lower first ionization potential and location in the electrochemical series allows it to be a useful antioxidant. However, it is one of the last molecules used by the human body to defend against damage from oxidation, as it is utilized even after Vitamin E. Melatonin is similar to Vitamin E in its ability to act as an electron donor or acceptor [27]. Unlike many antioxidants, melatonin is considered a terminal antioxidant, meaning that its is incapable of returning to its original condition after it has been oxidized.

Melatonin directly scavenges a multitude of free radicals. This ability was discovered less than thirty years ago. When melatonin interacts with free radicals, it forms metabolites. The metabolites formed by melatonin are actually capable of scavenging free radicals as well [28]. It is believed that melatonin may even be a better, more effective scavenger than Vitamin E and Vitamin C in many cases, despite the aforementioned similar properties to Vitamin E [25].

Additionally, melatonin tends to make many antioxidative enzymes more active. Therefore, it not only acts as an antioxidant, but also increases the activity and efficiency of other antioxidants. Melatonin achieves this by increasing the amount of mRNA in the other enzymes. It is not yet certain how melatonin is capable of affecting other enzymes in such a way. However, research is being conducted on the subject matter and some vague evidence exists. The little evidence suggests that it likely takes place in part because of certain receptors [25].

**Other Uses of Melatonin**

While melatonin has the ability to regulate sleep cycles, it can also help with other ailments to the body. The antioxidant properties of melatonin open up possibilities for other medical uses. While the long-term effects are relatively unknown, there are potential benefits for taking melatonin. However, according to the American Cancer Society, some users have reported headaches, drowsiness, and confusion, as well as trouble sleeping when taking melatonin at high doses [30]. In moderation, studies suggest that melatonin use can improve symptoms. You should consult your doctor before taking regular doses of melatonin. Not all of these studies were of appropriate size or quality to officially determine that melatonin should be used in each case. However, these studies prove that larger clinical trials would be useful, as the results show the advantageous properties of melatonin in small scale cases. See the appendix for more on macular degeneration and stroke protection.
Oxidative stress, which is an imbalance between the products of reactive oxygen species and antioxidant defenses, are involved in numerous medical conditions such as cardiovascular, neurological, and aging [41]. Oxidative stress is related to oxidation except it occurs in the body and damages material such as DNA and proteins. This damage causes degenerative diseases [42]. These prooxidants increase the number of harmful molecules in the body. The reactive oxygen species (ROS) are balanced out by the antioxidants. This imbalance is what causes oxidative stress. Antioxidants are used to combat these harmful ROS by natural sources in the body or man-made supplements.

Classical antioxidants often failed to exhibit beneficial effects, especially in degenerative diseases. Melatonin has been shown as a specific antioxidant due to its amphiphilic properties. Being amphiphilic means that melatonin can enter any bodily fluid, cell or cell compartment, making it a very versatile compound [43]. This helps to reduce the oxidative damage done in the body. Melatonin is also able to pick up multiple ROS. It does this by rearranging its chemical structure to continue to pick up more prooxidants as it moves through the body [45].

Alzheimer’s Disease Alleviation
Levels of naturally produced melatonin decline as people grow older. This leaves older adults with limited antioxidant protection against conditions such as neurodegenerative diseases. Melatonin supplements may help older adults enhance their antioxidant protection from diseases such as Alzheimer’s disease. A study done comparing melatonin levels in people with Alzheimer’s reported that melatonin levels are particularly low in patients with Alzheimer’s disease. Half of the affected individuals in the study suffered from sleep disturbances, confusion, and agitation mostly near evening times. Melatonin can benefit Alzheimer’s disease patients by improving sleep and late-night agitation. Melatonin has also been found to decrease cognitive deterioration in people with Alzheimer’s disease, possibly by protecting brain cells [36].

Cancer Prevention
Several studies suggest that low melatonin levels may be associated with a higher risk for breast cancer. Women with breast cancer tend to have lower levels of melatonin than those without the disease. Low levels of melatonin stimulate the growth of certain types of breast cancer cells [32]. In lab studies, melatonin appears to slow the growth of breast cancer cells. According to researchers from Henry Ford Hospital in Detroit, melatonin has the potential to reduce the growth of some types of cancer cells. To determine the effectiveness of melatonin on tumor growth, the researchers evaluated melatonin on ER-negative breast cancer in vitro and in vivo, with cells and mice [39]. The study found that none of the treated mice showed any loss of
weight and lethargy during the 21-day treatment. Instead, most showed excessive movement, but no irritability or aggressive behavior. Those treated showed significantly smaller tumors after 21 days. The results suggest that melatonin has the potential as a therapeutic agent for breast cancer [31].

**Melatonin Receptors**

Melatonin plays an important role in the circadian rhythm and brain functions. Melatonin contains receptors that control some brain functions. Chemical receptors are molecular structures located on the surface or interior of a cell that binds with substances such as hormones or neurotransmitters and are activated by certain events. Hormonal receptors are unique based on their chemical structure and their interactions with only certain hormones, in this case melatonin. The two main receptors of melatonin are MT₁ and MT₂. MT₁ is response for the suppressing the neuron firing rate. MT₂ is responsible for controlling the circadian rhythm phase changes. The addition of melatonin can enhance and regulate these receptors. These receptors are also found in other area of the body and can help regulate body systems and suppress other neurons, such as pain [44].

**Immune System Enhancement**

Melatonin has been linked to an improved immune system. Studies show there is enough evidence to confirm that melatonin interactions result in important regulatory effects for the immune system. The immune system also functions better when one’s circadian rhythm is aligned. The pineal gland, where the melatonin is produced, is part of the neuroendocrine system [15]. The neuroendocrine system has been shown to be linked to the immune system. The synchronization between melatonin production and seasonal adjustments in the immune system has been shown [33].

**Chronic Pain Reduction**

Melatonin has been shown to play an important role in the regulation of pain, since both pain perception and melatonin secretion are controlled by one’s circadian rhythm. Also,
Melatonin has been shown to influence pain perception. There is a strong relationship between sleep and headaches. The ability of melatonin to regulate sleep may also be useful in improving headache. In a study of 326 people with headaches and sleep disorders, 78.6% of people showed a decrease in their headaches and symptoms. This study demonstrated that 3 mg of melatonin before sleep can decrease the frequency, intensity, and duration of pain in migraine patients [34]. Another study was conducted involving 178 people who suffer from chronic back pain. This study showed that patients had less influence of pain in daily activities, a decrease in anxiety and depression, and sleep normalization while taking melatonin. That study confirmed that melatonin could decrease chronic back pain [35].

**Appendix**

**Albumin** - a protein in blood

**Antioxidant** - molecule that prevents cell damage from oxidation

**Blood-Brain Barrier**: a semi-permeable barrier in the brain where endothelial cells are so tightly packed that only certain molecules can transfer out of the bloodstream. The BBB protects the brain from foreign substances so that the brain does not get injured. Low lipid soluble molecules do not pass into the brain, but lipid soluble molecules, such as melatonin, pass rapidly [8,13].

**Catalyst** - speeds up reactions

**Cerebrospinal fluid**: the liquid around the brain and spinal cord [9].

**Circadian Rhythm** - internal clock controlled in the brain that cycles between sleepiness and alertness on a regular rhythm [11]

**Electrochemical Series** – elements arranged in order of electrode potential

**Electron Transfer Process** – when an electron transfers from one atom or molecule to another

**Endogenous melatonin** - natural hormone melatonin produced by the body

**Exogenous hormone** - melatonin taken into the body, usually as a supplement

**Enzyme** - biological catalyst

**First Ionization Potential** - the energy necessary to remove an electron with the highest energy to another location

**Fluvoxamine** - medication that functions as a selective serotonin reuptake inhibitor. It is mainly used to treat OCD but is also used to treat depression and anxiety disorders [22].

**In vivo** - in experiments, using live subjects, such as mice or humans [39]

**In vitro** - in experiments, using controlled cells outside of living subject [39]

**Lipid-soluble** - capable of dissolving in fats
**Macular Degeneration** - Macular degeneration is caused by the deterioration of the central portion of the retina, the inside back layer of the eye that records the images we see and sends them via the optic nerve from the eye to the brain. One research group explains that it is reasonable to think that the decrease in melatonin as age increases can be related to macular degeneration. One hundred patients with macular degeneration were given 3 mg of melatonin each night for six months. After six months sight levels had been kept stable. Only fourteen of the one hundred patients experienced worse degeneration. The MT2 receptor is also responsible for regulating several light dependent functions in the eyes.

**Metabolite** - a substance produced by or involved in metabolic processes

**mRNA** - messenger RNA, involved in DNA processes

**Oxidation** - loss of electrons or gaining of an oxygen atom

**Prooxidants** – induces oxidative stress either by generation of ROS or by inhibiting antioxidant systems

**Stroke Protection** - The brain can suffer irreparable damage when a person has a stroke. In a study using animal models, scientist have found that melatonin may be able to protect against stroke damage and deterioration. When administered at the time of stroke, melatonin limited the area of brain tissue damage, decreased brain cell death, and reduced the rate of stroke-related death. These scientists believe that melatonin may be able to improve the same stroke related symptoms in humans. Melatonin may also help in reducing a risk for stroke. Elevated blood pressure can be reduced at night time by taking melatonin. This study has been conducted with both men and women. While no daytime blood pressure change occurred, nighttime blood pressure was reduced without disturbing sleep. The circadian rhythm has been shown to be related to the regulation of the cardiovascular system, which regulates blood pressure.

**Tryptophan**- the amino acid that synthesises melatonin. Tryptophan must be taken up through ingestion, as it is not naturally produced in the body. The production of melatonin is significantly decreased if the intake of tryptophan is restricted.

**Vitiligo**- disease causing blotchy losses of skin color

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