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The Gravity of Weight

Melatonin: A Potential Disease-Deferring Hormone

Darkness Visible: In all plants and animals.

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KEY POINTS

- Melatonin, a hormone that regulates our body's circadian rhythms, is synthesized at night by the pineal gland.
- As a dietary supplement, it is not regulated by the FDA, and it is often misused as a sleeping pill.
- Melatonin has remarkable antioxidant and anti-inflammatory properties that may lead to new therapies.



Domenico Fetti, "Sleeping Girl," circa 1615. Museum of Fine Arts, Budapest

Source: Wikimedia Commons/Public Domain.

Legendary accounts of those who remain asleep for years fascinate us. There is Washington Irving's *Rip Van Winkle*, The Brothers Grimm's *Sleeping Beauty*, the Disney version of *Snow White*, and even the apocryphal tale of the *Seven Sleepers of Ephesus* who were walled in a cave in their attempt to escape Christian persecution, only to emerge 300 years later.

Perhaps these stories hold particular appeal because many people who long for that uninterrupted rest get considerably less sleep than recom-

mended, while others have difficulty remaining asleep.

Our Circadian Cycle

But neither too much sleep nor too little is beneficial for humans. It is the "consistency and integrity" of our sleep–wake cycle that is crucial for maintaining optimal health (Walker et al., 2022). As the earth rotates on its axis around the sun, the body's biological rhythms, including the secretion of many hormones, are synchronized to an approximate 24-hour (i.e., circadian) day-night/light-dark cycle. Our built-in master clock, the suprachiasmatic nucleus (SCN) in our anterior hypothalamus, regulates this system.

Though food, exercise, and temperature can affect circadian rhythms, light is the strongest "timekeeper" (Walker et al.). (For more on sleep and circadian rhythms, see my previous posts,

[Time Present and Time Past: Obesity and Chronobiology](#) and [The Long and the Short of It: Sleep Duration and Health](#)).

Even the Bible, in its initial verses, underscores the importance of our day/night cycle: One of God's first acts was to separate light from darkness (Genesis 1:3-5).

The Hormone of Darkness

Melatonin, often referred to as the "hormone of darkness," is a "circulating messenger" that links the SCN with the body and other parts of the brain (Walker, 2017).



"Dividing Light from Darkness," from the High Altar of St. Peter's in Hamburg, 1383.

Source: Courtesy of Bridgeman images.



"Plague of Darkness," French School, 13th century.
Sainte-Chapelle, Paris.

Source: Courtesy of Bridgeman images.

It is an ancient molecule, at least 2.5 billion years old, that has been found in every species—plant or animal—that has been investigated (Suriagandhi and Nachiappan, 2022).

Levels of melatonin, synthesized in the pineal, a small gland deep in the brain, begin to rise at dusk, peak by 4 a.m., then fall and are not detectable by early to midmorning (Walker, 2017).

Another noncirculating pool of melatonin, "probably" produced within the mitochondria of many cells in the body is responsible for many of melatonin's therapeutic effects. This pool, which does not exhibit a circadian rhythm, may be a "critical factor" in the optimal

functioning of mitochondria (Reiter et al., 2022).

Though neither John Milton nor T.S. Eliot knew anything about melatonin, which was isolated in 1958 (Wurtman, 1985), each wrote of darkness: Milton, of "darkness visible" (*Paradise Lost*), and Eliot, "O dark dark dark...Let the darkness come upon you (*Four Quartets*).

There can, though, be too much darkness. Plunging the earth for only three days into total darkness (Exodus 10: 21-29) became the ninth plague inflicted upon the ancient Egyptians.

"Darkness is a human concept" that is often poorly quantified and "under-appreciated." The level of darkness, for example, can be crucial and imprecisely measured. Furthermore, since animals in the wild experience some light from the moon or stars, creating an extremely dark environment may not mimic nature (Aulsebrook et al., 2022).

In our 24/7 world of artificial light, including computer screens and smartphones, though, we are more apt to suffer from *light pollution* than the plague of total darkness. Melatonin secretion is exquisitely sensitive to light exposure, particularly light in the blue spectrum, typical of our white lights. Since "light is light," whether natural or artificial, most light suppresses melatonin secretion immediately (Walker et al.). The exception is light emanating from the moon, which is in the yellow and red spectrum.



van Gogh, "Starry Night over the Rhone," 1888. Musee d'Orsay, Paris.

Source: Courtesy of Bridgeman Images.

Songwriter Paul Simon captures the sensitivity of melatonin to light perfectly when he wrote of the "eye being stabbed by the flash of a neon light" (*Sound of Silence*, 1963).



Lamplight, 1908, by French artist Jules Emile Crochet. Private Collection. With the use of artificial lights, we are more apt to suffer from light pollution than from too much darkness.

Source: Courtesy of Christie's Images/Bridgeman Images.

Effects of Melatonin

As well as being responsive to light, melatonin has other remarkable effects. It has potent antioxidant and anti-inflammatory properties, and there is even a suggestion it may have some role in leptin signaling and treating leptin resistance (Suriagandhi and Nachippan). Furthermore, it has major anti-cancer effects: it is *oncostatic*, namely—it can suppress cancer growth in some tumors and even suppress the development of metastases (Reiter et al., 2021a; Mu and Najafi, 2021). It may also work synergistically with anti-

cancer agents to produce less toxicity (Gurunanthan et al., 2021). Melatonin reportedly has a role in the treatment of osteoporosis (López-Muñoz et al., 2022). Reiter, a major researcher in this field, and his colleagues refer to melatonin as a "disease-deferring" hormone (2021b).

As we age, our levels of melatonin fall dramatically. Some researchers theorize that these decreased levels may make us more vulnerable to the diseases of aging or even that they may be a biomarker for the development of age-related diseases, including cancer (Giménez et al., 2022). They suggest that exogenous supplementation with this "multi-tasking molecule," with its anti-inflammatory properties, may eventually be an "anti-aging therapy" for cardiovascular and neurodegenerative diseases, although an optimal dose has yet to be established (Bocheva et al., 2022; Tobeiha et al., 2022; Giménez et al.).

Exogenous melatonin given to increase blood levels can be administered orally (sustained or immediate release), sublingually, intranasally, intravenously, by skin patch, and even rectally by suppository (Reiter et al., 2021b). Typical oral doses range from 1 mg to 10 mg at bedtime.

The use of melatonin has skyrocketed in recent years, even though it is not a medication for insomnia but rather for realigning the body's circadian rhythms, such as with jet lag. It has raised safety concerns, especially with long-term use in certain populations like children and adolescents (Kuehn, July 2022).

There are some contradictory reports that melatonin may have endocrinological effects, such as on glucose or the sex hormones in both men and women (Foley and Steel, 2019) or even on the timing of puberty (Besag et al., 2019).



"Boy in bed afraid of the dark," 1932. American School. Vintage illustration.

Source: Courtesy of GraphicaArtis/Bridgeman Images.

In the United States, it has been available as a dietary supplement since 1994 (Kennaway, 2022). As such, it is often self-prescribed, used "off-label," and can be obtained over the counter with no Food and Drug Administration quality control (Foley and Steel). In most countries, melatonin requires a prescription (Kuehn).



Moonlit woodland scene, 19th century. Ottoman School/Turkish. Private Collection.

Source: Courtesy of Bridgeman Images.

Systematic reviews to evaluate safety often involve different formulations, different treatment durations, or even undisclosed conflicts of interest (Besag et al.). There is, though, no known life-threatening dose (Besag et al.), but adverse effects include vivid dreams, headache, fatigue, dizziness, or daytime sleepiness that may occur when melatonin is used incorrectly (Kuehn).

Furthermore, differentiating adverse *events* from adverse *effects* is particularly difficult when patients take other medications simultaneously that may interact with the metabolism of melatonin (Besag et al.; Foley and Steel; Kennaway).

Though melatonin is often misused as a medication for insomnia, research indicates it has remarkable potential as a "disease-deferring" hormone.

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