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UPDATE

Mainstream Melatonin

THE GOAL: TO FIND PRACTICAL METHODS OF RETARDING THE AGING PROCESS

Review in New England Journal of Medicine Cites Benefits on Sleep, Tumors and More

In the Jan. 16, 1997, issue of *The New England Journal of Medicine (NEJM)*, there is a 10 page review article on melatonin . . . the most extensive overview about melatonin that has ever been published in a conventional medical journal.

The *NEJM* article extols the many virtues of melatonin, including its powerful antioxidant effects, its potential benefit in preventing and treating cancer, its immune enhancement properties, its potential to slow aging, and its ability to promote better sleep and to avoid jet lag.

"There is now evidence," notes the *NEJM*, "that melatonin may have a role in the biologic regulation of circadian rhythms, sleep, mood, and perhaps reproduction, tumor growth and aging. . . ."

The only real difference between articles on melatonin that have appeared in Life Extension magazine and the article in *The New England Journal of Medicine* are the conclusions. The Foundation recommends supplemental melatonin for most people while the *NEJM* article, after laying out the many benefits of melatonin, concludes that, "uncontrolled use of melatonin to obtain any of these [beneficial] effects is not justified."

This conclusion shouldn't be surprising. Medical journals are almost always extremely conservative in their recommendations. The December 25, 1996, issue of the *Journal of the American Medical Association (JAMA)*, for example, reported that selenium supplements reduced cancer mortality by 50 percent in humans in a long-term double-blind, controlled study. Yet the conclusion of the *JAMA* study was, "It is premature to change individual behavior." In other words, don't take selenium supplements yet!

A contradiction appearing in the *NEJM* article on melatonin was its criticism of people who ingest more than 300 to 500 mcg a night of melatonin, thus increasing their serum levels by 10 to 100 times the normal level found in a young person. Yet, throughout the article, the author states that these high doses (1 to 5 mg a night) are needed to obtain the many health benefits attributed to melatonin.

Here are verbatim excerpts from the *NEJM* article:

EFFECTS ON CANCER

"There is evidence from experimental studies that melatonin influences the growth of spontaneous and induced tumors in animals. Pinealectomy enhances tumor growth, and the administration of melatonin reverses this effect or inhibits tumorigenesis caused by carcinogens.

"Data on the relation between melatonin and oncogenesis in humans are conflicting, but the majority of the reports point toward protective action. Low serum melatonin concentrations and low urinary excretion of melatonin metabolites have been reported in women with estrogen-receptor-positive breast cancer and men with prostatic cancer.

"The mechanism by which melatonin may inhibit tumor growth is not known. One possibility is that the hormone has antimetabolic activity. Physiologic and pharmacologic concentrations of melatonin inhibit the proliferation of cultured epithelial breast cancer



cell lines (particularly MCF-7) and malignant melanoma cell lines (M-6) in a dose-dependent manner. This effect may be the result of intranuclear down-regulation of gene expression or inhibition of the release and activity of stimulatory growth factors. Melatonin may also modulate the activity of various receptors in tumor cells.



"For example, it significantly decreased both estrogen-binding activity and the expression of estrogen receptors in a dose-specific and time-dependent manner in MCF-7 breast cancer cells. Another possibility is that melatonin has immunomodulatory activity. In studies in animals, melatonin enhanced the immune response by increasing the production of cytokines derived from T-helper cells (interleukin-2 and interleukin-4), and as noted earlier, in mice melatonin protects bone marrow cells from apoptosis by enhancing the production of colony-stimulating factor by granulocytes and macrophages.

"Lastly, as a potent free radical scavenger, melatonin may provide protection against tumor growth by shielding molecules, especially DNA, from oxidative damage. However, the antioxidant effects of melatonin occur only at very high concentrations.

(Editor's note: The *NEJM* defines high concentrations of melatonin as 1-5 mg per night.)

"The effects of melatonin have been studied in some patients with cancer, most of whom had advanced disease. In these studies, melatonin was generally given in large doses (20 to 40 mg per day orally) in combination with radiotherapy or chemotherapy. In a study of 30 patients with

glioblastomas, the 16 patients treated with melatonin and radiotherapy lived longer than the 14 patients treated with radiation alone. In another study by the same investigators, the addition of melatonin to tamoxifen in the treatment of 14 women with metastatic breast cancer appeared to slow the progression of the disease. In a study of 40 patients with advanced malignant melanoma treated with high doses of melatonin (up to 700 mg per day), 6 had transient decreases in the size of some tumor masses. It has been claimed that the addition of melatonin to chemotherapy or radiotherapy attenuates the damage to blood cells and thus makes the treatment more tolerable. All these preliminary results must be confirmed in much larger groups followed for longer periods of time."

(Editor's note: Medical journals often use the term "chemotherapy" either for cytotoxic [cell poisoning] therapy, or for immune-enhancing therapies such as interleukin-2 or interferon that are far less toxic.)

FREE RADICAL SCANVENGING

"Both in vitro studies and in vivo studies have shown that melatonin is a potent scavenger of the highly toxic hydroxyl radical and other oxygen-centered radicals, suggesting that it has actions not mediated by receptors. In one study, melatonin seemed to be more effective than other known antioxidants (e.g., mannitol, glutathione, and vitamin E) in protecting against oxidative damage.

Therefore, melatonin may provide protection against diseases that cause degenerative or proliferative changes by shielding macromolecules, particularly DNA, from such injuries. However, these antioxidant effects require concentrations of melatonin that are much higher than peak nighttime serum concentrations. Thus, the antioxidant effects of melatonin in humans probably occur only at pharmacologic concentrations." (Editor's Note: The *NEJM* defines pharmacological doses of melatonin as 1-5 mg a night.)

IMMUNE FUNCTION

"Melatonin may exert certain biologic effects (such as the inhibition of tumor growth and counteraction of stress-induced immunodepression) by augmenting the immune response. Studies in mice have shown that melatonin stimulates the production of interleukin-4 in bone marrow T-helper cells and of granulocyte-macrophage colony-stimulating factor in stromal cells, as well as protecting bone marrow cells from apoptosis induced by cytotoxic compounds. The purported effect of melatonin on the immune system is supported by the finding of high-affinity (K_d , 0.27 nM) melatonin receptors in human T lymphocytes (CD4 cells) but not in B lymphocytes."

IMPACT ON SLEEP

". . . Ingestion of melatonin affects sleep propensity (the speed of falling asleep), as well as the duration and quality of sleep, and has hypnotic effects. In young adults, oral administration of 5 mg of melatonin caused a significant increase in sleep propensity and the duration of rapid-eye-movement (REM) sleep. In other studies, sleep propensity was increased in normal subjects given much lower doses of melatonin (0.1, 0.3, or 1 mg), either in the daytime or in the evening, and sleepiness in the morning was not increased. The time to the maximal hypnotic effect varies linearly from about three hours at noon to one hour at 9 p.m. The administration of melatonin for three weeks in the form of sustained-release tablets (1 mg or 2 mg per day) may improve the quality and duration of sleep in elderly persons with insomnia.

"These results indicate that increasing serum melatonin concentrations (to normal nighttime values or pharmacologic values) can

trigger the onset of sleep, regardless of the prevailing endogenous circadian rhythm. The hypnotic effect of melatonin may thus be independent of its synchronizing influence on the circadian rhythm and may be mediated by a lowering of the core body temperature. This possibility is supported by the observations that the circadian cycle of body temperature is linked to the 24-hour cycle of subjective sleepiness and inversely related to serum melatonin concentrations and that pharmacologic doses of melatonin can induce a decrease in body temperature. However, physiologic, sleep-promoting doses of melatonin do not have any effect on body temperature. Alternatively, melatonin may modify brain levels of monoamine neurotransmitters, thereby initiating a cascade of events culminating in the activation of sleep mechanisms. . . .

"Exogenous melatonin thus appears to have some beneficial effects on the symptoms of jet lag, although the optimal dose and timing of ingestion have yet to be determined. It is also unclear whether the benefit of melatonin is derived primarily from a hypnotic effect or whether it actually promotes a resynchronization of the circadian rhythm. . . .

"Low nighttime serum melatonin concentrations have been reported in patients with depression, and patients with seasonal affective disorder have phase-delayed melatonin secretion."

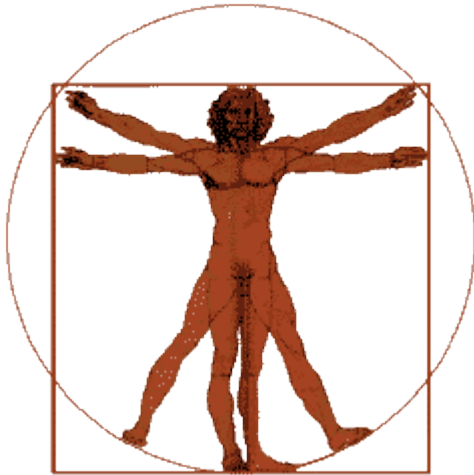
(Editor's note: Some people who suffer from seasonal affective disorder [SAD] may want to reduce or eliminate melatonin supplementation during the dark months of the year.)

A ROLE IN AGING

"The decrease in nighttime serum melatonin concentrations that occurs with aging, together with its multiple biologic effects, has led several investigators to suggest that melatonin has a role in aging and age-related diseases. Studies in rats and mice suggest that diminished melatonin secretion may be associated with an acceleration of the aging process. Melatonin may provide protection against aging through attenuation of the effects of cell damage induced by free radicals or through immunoenhancement. However, the age-related reduction in nighttime melatonin secretion could well be a consequence of the aging process rather than its cause, and there are no data supporting an anti aging effect of melatonin in humans."

NEJM'S CONCLUSIONS

"There is now evidence to support the contention that melatonin has a hypnotic effect in humans. Its peak serum concentrations coincide with sleep. Its administration in doses that raise the serum concentrations to levels that normally occur nocturnally can promote and sustain sleep. Higher doses also promote sleep, possibly by causing relative hypothermia. Exogenous melatonin can also influence circadian rhythms, thereby altering the timing of fatigue and sleep. . . .



"It is tempting to speculate that the hormone also has antigonadal or antioviulatory effects in humans, as it does in some seasonal and nonseasonal mammalian breeders, but this possibility has not been substantiated. The antiproliferative and anti-aging effects of melatonin are even more problematic. Uncontrolled use of melatonin to obtain any of these effects is not justified."

(Editor's note: Very high doses of melatonin [75 mg] are being used as a birth control pill in Europe.)

The Foundation's Conclusions

The human race is afflicted with chronic, degenerative diseases and the inexorable deterioration of aging. If published scientific studies show that a natural hormone supplement can boost immune function, scavenge free radicals, fight cancer, induce youthful sleep patterns and possibly slow aging, then we think most people should be taking this hormone.

The average reader of Life Extension magazine is "programmed" by nature to die within 35 years. Any supplement that can help prevent lethal diseases, extend average lifespan in animals and improve sleep should be recommended for widespread public use.

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