

REPORT

Why Researchers at Cancer Treatment Centers of America Are
Investigating Melatonin
as an Anti-Aging Therapy in Cancer Treatment

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Despite the many advances in our knowledge and treatment of cancer, medicine has encountered many barriers that limit the effectiveness of conventional cancer treatment today. While our five-year survival and mortality rates appear to be improving, some cancer epidemiologists contend that these trends are an artifact of improvements in diagnostic technology. While advances have led to an earlier age at diagnosis, the age-specific mortality rates for most adult tumor patients has remained relatively stable during the past 30 years. As such, we are detecting tumors earlier in the disease course, but often, the fate of the many patients remains unaltered. Thus, it appears that medicine has exhausted the benefits of standard conventional therapy in much of adult cancer (Greaves, 2000).

Clearly, the aging process confounds the benefits of conventional cancer treatment, and current therapy has failed to overcome the impact of aging on the effectiveness of care. During the aging process, there is a progressive decline in response to therapy as a function of age. In fact, in adults over 45 years, response to therapy drastically diminishes with increasing age for many types of cancer patients. Because most cancer patients are over 45 years, there is an urgent need to address the impact of aging on the effectiveness of treatment (Latif, 1998).

Currently, the most promising anti-aging therapy is melatonin, a ubiquitous circadian and circannual time keeping hormone, found in multi-cellular organisms, ranging from algae to mammals. During the last two decades, researchers have made important discoveries about melatonin's therapeutic properties (Pierpaoli et al., 1993). In this article, we will discuss the evolving evidence of melatonin's role as an adjuvant therapy for adult cancer.

Insights from evolutionary medicine show that aging is an inescapable feature of the human life cycle. In previous generations, infectious diseases, childbirth and accidents have governed life span. In the modern world, these evolutionary constraints have been greatly reduced in industrialized countries, yet, the biology of aging has been unaltered.

During most of human evolution, the vast majority of people died long before they had the opportunity to develop the diseases of old age. The forces of natural selection allocate sufficient biologic resources for reproduction. Until recently, death from environmental hazards was inevitable by age fifty. Consequently, there was no reason to allocate biologic resources to maintain a body well into old age. The forces of natural selection have, therefore, provided human beings with resilience against disease during a time period of optimal reproduction (Olshansky and Carnes, 2001).

Unfortunately, many physiologic processes that promote health early in life often cause disease decades later. To illustrate, the acute inflammatory response caused by bacterial infection maintains health and well-being in the young. However, over time this protective mechanism also damages the endothelial cells that line our blood vessels. Thus, the cascade of events that maintain health early in life progressively predispose middle aged and older adults to various forms of cardiovascular disease.

Is the pineal gland the aging clock?

The central aging clock most likely evolved from the biochemical mechanisms of intercellular communication. The regulation of cell, tissue and organ behavior is largely under the control of extracellular chemical signals. These chemical signals induce the appropriate behavior at supra threshold concentrations. Most biological signals are produced as surges in levels; consequently,

most cell behaviors are induced after the amplitude of the pulse exceeds the threshold concentration. Thus, a complex network of pulsating chemical signals regulates the complicated physiological economy of the body. When these signaling networks decay, the processes of self-repair and regeneration needed to preserve optimal biological function fail.

There are scientific observations that link the pineal gland's production of melatonin to an "aging clock." Melatonin is a chronobiologic agent produced by the pineal gland, whose chemistry is both lipophilic and hydrophilic. It easily diffuses through all bio-barriers including the blood-brain and placenta. Therefore, unlike other extracellular signals, melatonin is available to all the tissues of the body, including fetal. An ever-increasing body of experimental data shows that there are receptors for melatonin in most tissues of the human body, including neoplastic tissue (i.e. cancer cells) (Olcese, Melatonin After Four Decades, 1999). Interestingly, the nocturnal surge of melatonin is linked to the nocturnal release of growth hormone, insulin-like growth factors and other agents associated with tissue repair, maintenance and self-regeneration. These findings suggest that melatonin is an ideal candidate for the aging clock in humans.

In young adults, the serum melatonin levels surge in the early evening hours, peak in the middle of the night, and decline as dawn approaches. There are observations that link a sudden decrease in melatonin amplitude with the onset of puberty in humans. As human's age, there is an attenuation in melatonin's serum nocturnal surge—a process hypothesized to regulate the aging process. As we age, the peak amplitudes of many growth factors, hormones and other extracellular chemical signals decline sharply. In animal bioassays, Maestroni's group has shown that implanting youthful pineal glands in older animals prolongs life span, while maintaining youthful behavior in mice. In addition, the nocturnal administration of melatonin to the drinking water of mice prolonged life span by 25% and forestalled the telltale signs of aging in these animals.

Melatonin: a chronobiologic agent

Circadian rhythms governing the biochemical and cellular economy of our bodies evolved from the capacity to measure and respond to the duration of daylight. Consequently, vertebrates use this information to organize their activities of normal life. Information on the photoperiod is transmitted to the organs of the body, whereby these stimuli control the synthesis and release of melatonin.

Melatonin's circadian rhythm communicates the stage of the circadian cycle to all the body's cells.

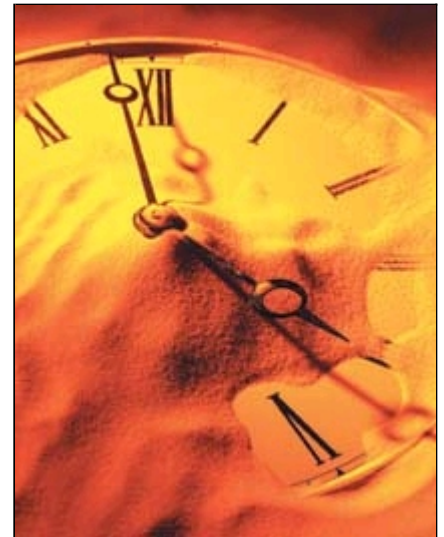
Thus, melatonin coordinates an organism's physiologic activities of daily living. In mammals, melatonin is mainly produced in the pineal gland, whose function is converting the changes in light intensity into a nighttime pulse of melatonin. The nocturnal pulse of melatonin is the pacemaker organizing the diverse circadian rhythms that regulate an animal's daily activities, as well as its seasonal reproductive behavior. Data from many investigators have correlated melatonin levels with a host of biologic processes, including circadian rhythmicity, mood, sexual maturation and reproduction, immune function and aging (Brzezinski, 1997).

Not surprisingly, there is a significant body of clinical research demonstrating that melatonin promotes sleep. Lerner, the discoverer of melatonin, reported that it had a soporific effect (Lerner et al., 1958). Clinical trials have demonstrated that nighttime doses of melatonin shorten sleep latency, prolong its duration and increase REM sleep (Dawson and Encel, 1993; Zhdanova et al., 1995). Interestingly, melatonin's sleep inducing activities are circadian phase-dependent, e.g., exogenous melatonin administration does not induce sleep when given in the morning.

Melatonin regulates core body temperature. Body temperature follows a circadian rhythm and the lowest temperature coincides when sleep occurs. Administering melatonin to subjects during the day will lower the daily peak temperature by 0.3 C, whereas blocking evening melatonin secretion eliminates the reduction in core body temperature (Hrushesky, 2001). The hypothesized mechanism of action is that melatonin accelerates heat loss by dilating peripheral blood vessels. These investigations used individuals who underwent 24-hour bed rest (Cagnacci et al., 1997).

Melatonin as anti-cancer therapy

Despite the many innovations that have occurred in cancer medicine, the age specific mortality for most adult tumors has remained stable during the past thirty years (Greeves, 2000). There have been clinically significant improvements in the outcomes of young and middle aged patients, yet the vast majority of cancer patients are over 50 years of age, of which we observe few improvements in overall clinical outcomes. This evidence suggests that the aging process limits the therapeutic benefits of



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An example of the relationship between age and response to therapy can be found in patients with mid-grade brain tumors. Twenty years ago, the median survival of these patients ranged from one to two years. Today, in patients younger than 45 years, survival ranges between 8 to 11 years. However, in patients greater than 45 years, survival declines at an accelerating rate with increasing age. Indeed, the survival of 65-year-old mid-grade astrocytoma patients is only 8 to 11 months, versus 8 to 10 years in patients below 45 years. This astounding clinical observation illustrates the importance of age as it relates to response to therapy in cancer patients.

Because melatonin has all the features of an aging clock, it is an ideal candidate for therapeutic intervention in age-dependent processes. Melatonin's anti-aging properties derive from its capacity to integrate the diurnal rhythms that organize the daily activities of our lives. Unfortunately, for most tumor patients, melatonin circadian rhythm has diminished and concomitantly, the diurnal physiological rhythms involved in tissue repair and regeneration are either in decline or have disappeared (Greaves M, 2000).

Fortunately, there are data indicating that melatonin replacement therapy restores the circadian rhythms of other physiological processes (e.g. growth hormone, DHEA etc.) (Brzezinski, 1997). Investigations in animals suggest that replacement melatonin therapy lowers the rate of carcinogen-induced tumor formation and prolongs life span. Melatonin's anti-aging benefits are found in a variety of experimental animal systems. These experiments show that abolishing melatonin's circadian rhythm accelerates the signs of aging, shortens life span, and elevates the spontaneous tumor rate (Maestroni et al., 1988).

The medical literature reports that melatonin produces a variety of favorable outcomes in oncology patients (please see Table 1 for summary). Lissoni's group reports that melatonin reduces the toxicity of various chemotherapeutic agents, including cisplatin, etoposide, anthracyclines and 5-fluorouracil. In addition, they found a statistically significant reduction in treatment related adverse events, such as myelosuppression, neurotoxicity, nephrotoxicity, cardiotoxicity and asthenia. In other trials, Lissoni's group reports that melatonin treated patients experienced relief of anxiety and improvement in the quality of sleep. These investigators also report that melatonin may counteract the body wasting that occurs with progressing cancer and forestalls respiratory distress (Lissoni P, Paolorossi F, Tancini G, 1996).

Moreover, melatonin appears to reduce the side effects of radiotherapy. In a small-randomized trial of grade 4 astrocytoma patients, investigators discovered that melatonin improved quality of life and survival compared to radiotherapy alone. Indeed, in their many publications, Lissoni et al. found no melatonin-related toxicity (Lissoni et al., 1992, 1994, 1996, 1999). In another investigation, Gonzalez et al report that 700-mg doses of melatonin induced transient decreases in the tumor mass of patients with advanced malignant melanoma.

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Lissoni's (1999) researchers report anecdotal evidence that the patients receiving melatonin experience a relief of anxiety, improved quality of life and overall improvements in patient function and well-being. They also report that melatonin diminishes blood cell damage induced by conventional radiotherapy and chemotherapy. Moreover, they report that melatonin forestalls weight loss in patients with advanced disease.

Melatonin has been shown effective in inducing sleep in healthy subjects. Melatonin is recognized to have a hypnotic effect at pharmacologic doses and causes an increased propensity to sleep, as demonstrated in placebo-controlled clinical trials. Published studies have found that ingestion of melatonin increases the speed of falling asleep, the duration of sleep and the quality of sleep (Dawson and Encel, 1993; Zhdanova et al., 1995).

Melatonin may have an effect on mood. Depression is a common problem in patients with advanced cancer. Patients with depression (as are patients with advanced cancer) are found to have low nighttime serum melatonin concentrations (Brown et al., 1987). Because many cancer patients have disruptive sleep patterns and experience depression, melatonin's role as a supportive agent requires further investigation.

Table 1. Lissoni's Phase II Randomized Clinical Trial Results

TumorType	Patient Number	Comparison	Melatonin Dose	One Year Survival		Level Of Significance
				Melatonin	Placebo	
Metastatic Non Small Cell Lung	63	Supportive Care Only	10 mg	26%	Under 1%	<0.05
Glioblastoma	30	Conventional Radiotherapy	10 mg	43%	Under 1%	<0.05
Metastatic Breast	40	Tamoxifen	20 mg	63%	24%	<0.01
Brain Metastases	50	Conventional Radiotherapy	20 mg	38%	12%	<0.05
Metastatic Colorectal	50	IL-2	40 mg	36%	12%	<0.05
Metastatic Non Small Cell Lung	60	IL-2	40 mg	45%	19%	<0.05

The need for further research on melatonin therapy in cancer

We still have relatively little understanding of how melatonin works in the human body. Many questions have been raised, but few have been answered. The long-term effects of chronic melatonin use are currently unknown.

Despite the broad public interest in melatonin and other complementary therapies, there is only modest funding for clinical investigations in melatonin research. American and European governments finance some basic research on melatonin, yet, very little funds have been allocated to investigate the clinical implications of melatonin therapy in the management of chronic disease.

These issues have compelled investigators at Cancer Treatment Centers of America (CTCA) to develop cancer trials that address the most critical issues involving melatonin's use in cancer patients. In doing so, CTCA has also partnered with two renowned experts in the field of melatonin therapy and chronobiology, David E. Blask, MD, PhD from the Bassett Research Institute at Mary Imogene Bassett Hospital and William JM Hrushesky, MD of the University of South Carolina School of Medicine, respectively. Interestingly, Dr. Blask was the discoverer of melatonin's role in breast cancer, and Dr. Hrushesky has made major discoveries in applying the science of chronobiology to cancer treatment.

Currently, most of the data on the benefits of melatonin on cancer patients comes from Lissoni's center in Italy. These researchers have steadily produced results showing that melatonin has a role in cancer therapy. The trials in Italy have been small, but nonetheless, produced provocative results. These studies involved small numbers of patients and collected insufficient high quality data on a variety of clinical issues to measure melatonin's true benefits in cancer. For these reasons, the medical community does not accept the Lissoni's data as definitive. Cancer researchers at CTCA are hoping to confirm and significantly extend Lissoni's most interesting findings in a large-scale multi-center trial conducted in the United States.

Investigators at CTCA have addressed the design shortcomings found in the literature with several innovations. First, the study is investigating whether the circadian activity/rest rhythms in cancer patients is normal or abnormal prior to melatonin therapy. Surprisingly, this will be the first trial ever to investigate: (1) whether cancer patients produce a nocturnal pulse of melatonin prior to therapy, and (2) what fraction of patients with advanced cancer suffer abnormalities in their circadian activity/rest rhythm. This information will provide physicians and researchers with insight on why patients are unable to complete or respond to therapy.

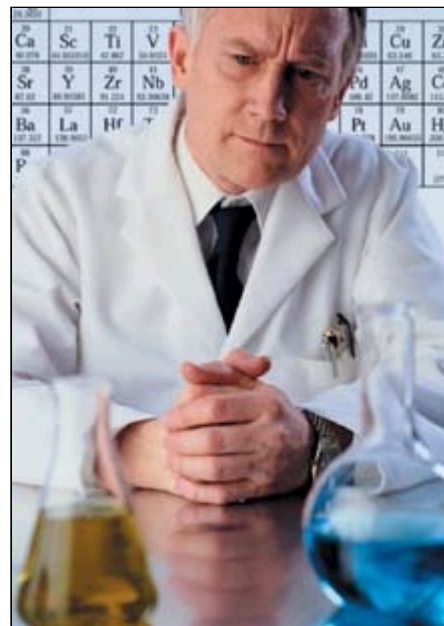
Second, CTCA is investigating the therapeutic dose of melatonin required to induce its known biological effects in cancer patients undergoing chemotherapy. Consequently, physicians will know whether the patient was exposed to a biologically effective dose of melatonin. These findings will also be the first to report on the absorption and degradation of oral melatonin in patients undergoing chemotherapy.

Third, CTCA is looking at melatonin's therapeutic benefits at two distinct phases of the circadian cycle—diurnal and nocturnal. Lissoni's group investigated nocturnal doses of melatonin, while Gonzalez's group in Colorado had patients take melatonin every four hours (a non-chronobiologic dosing pattern).

Finally, investigators at CTCA are using validated instruments that accurately measure health-related quality of life, sleep quality and fatigue in patients undergoing melatonin treatment with chemotherapy.

If melatonin lives up to its promise, cancer treatment will be drastically improved by reduced treatment-related toxicity, improved quality of life and increased long-term survival. This exciting research will also provide the necessary clues on melatonin's role as an effective anti-aging therapy in humans.

For more information about Cancer Treatment Centers of America's integrative care, call Oncology Information Specialist, Doug White at 1-800-577-1255.



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